26 January 2017
EMA/106922/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AMGEVITA

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/004212/0000

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ACR20	20% improvement in ACR core set measurements
ACR50	50% improvement in ACR core set measurements
ACR70	70% improvement in ACR core set measurements
ADA	Antidrug antibody
Adalimumab (EU)	Humira® which is approved and marketed in the European Union
Adalimumab (US)	Humira® which is approved and marketed in the United States
ADCC	Antibody-dependent cell-mediated cytotoxicity
AI	Autoinjector
ALT	Alanine amino transferase
AS	Ankylosing spondylitis
AUC	Area under the serum concentration-time curve
AUC_{inf}	Area under the serum concentration-time curve from time 0 to infinity
AUC_{last}	Area under the serum concentration-time curve from time 0 to the last quantifiable concentration
BMWP	Biosimilar medicinal products working party
BSA	Body surface area
CBER	Center for Biologics Evaluation and Research
CD	Crohn's disease
CDC	Complement-dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human use
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum serum concentration
CSR	Clinical study report
DAS28-CRP	Disease Activity Score 28 – C-reactive protein
ECL	Electrochemiluminescent
ELD	Evaluation and Licensing Division
EMA	European medicines agency
EOI	Event of interest
EPAR	European public assessment report
EU	European union
FAS	Full analysis set
Fc	Fragment crystallizable
FcR	Fc receptor
FcRn	Neonatal Fc receptor
FcγRIa	Fragment crystallizable gamma receptor Type Ia
FcγRIIa	Fragment crystallizable gamma receptor Type IIa
FcγRIIIa	Fragment crystallizable gamma receptor Type IIIa
FDA	Food and Drug Administration
GCP	Good clinical practice
GLP	Good laboratory practice
GMR	Geometric mean ratio
HS	Hidradenitis suppurativa

HUVEC	Human umbilical vein endothelial cells
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonisation
IL-8	Interleukin-8
IP	Investigational product
JIA	Juvenile idiopathic arthritis
LOCF	Last observation carried forward
LTα	Lymphotoxin alpha
mAb	Monoclonal antibody
mbTNFα	Transmembrane tumor necrosis factor alpha/membrane-associated tumor necrosis factor alpha
MCP-1	Monocyte chemotactic protein-1
MHLW	Ministry of Health, Labour, and Welfare (Japan)
MIP-1β	Macrophage inflammatory protein-1 beta
MLR	Mixed lymphocyte reaction
MOA	Mechanism of action
MTX	Methotrexate
NHP	Nonhuman primate
PASI	Psoriasis Area and Severity Index
PASI 50	≥ 50% improvement in PASI
PASI 75	≥ 75% improvement in PASI
PASI 90	≥ 90% improvement in PASI
PASI 100	Total clearance of psoriasis
PD	Pharmacodynamic(s)
PFS	Prefilled syringe
PFSB	Pharmaceutical and Food Safety Bureau (Japan)
PK	Pharmacokinetic(s)
PP	Per protocol
Ps	Plaque psoriasis
PsA	Psoriatic arthritis
Q2W	Every 2 weeks
RA	Rheumatoid arthritis
SBP	Similar biotherapeutic product
SC	Subcutaneous(ly)
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
sPGA	Static Physician's Global Assessment
sTNFα	Soluble tumor necrosis factor alpha
TK	Toxicokinetic(s)
TNFα	Tumor necrosis factor alpha
TNFRSF	Tumor necrosis factor receptor superfamily
TNFRSF1A	Tumor necrosis factor receptor superfamily 1A
TNFRSF1B	Tumor necrosis factor receptor superfamily 1B
UC	Ulcerative colitis
US	United states
w/v	Weight/volume
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 3 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for AMGEVITA, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2015.

The applicant applied for the following indication:

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 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 to improve 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 13 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (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.

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 nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

AMGEVITA is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug 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 failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

Paediatric plaque psoriasis

AMGEVITA is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents weighing 47 kg and greater 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 adult patients with an inadequate response to conventional systemic HS therapy.

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 severe 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, a corticosteroid, and 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.

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with

authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen **reference product** is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Humira 40 mg/0.8 ml solution for injection in vial and pre-filled syringe
- Marketing authorisation holder: AbbVie Ltd.
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/03/256/001-002

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

- Product name, strength, pharmaceutical form: Humira 40 mg and 40 mg/0.8 ml solution for injection in vial, pre-filled syringe, and pre-filled pen
- Marketing authorisation holder: AbbVie Ltd.
- Date of authorisation: 08-09-2003, 07-11-2006, 18-03-2011
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/03/256/001-014

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which comparability tests have been concluded:

- Product name, strength, pharmaceutical form: Humira 40 mg solution for injection in pre-filled syringe
- Marketing authorisation holder: AbbVie Ltd.
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number(s): EU/1/03/256/002-004
- Bioavailability study number(s): 20110217

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17/11/2011 and 18/10/2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 3 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 1 April 2016.
- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 29 April 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 July 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 August 2016.
- During the PRAC meeting on 2 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 November 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 November 2016.
- During the CHMP meeting on 15 December 2016, the CHMP agreed on the 2nd List of outstanding issues to be addressed in writing.
- The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 22 December 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 January 2017.
- During the meeting on 23-26 January 2017, 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 26 January 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

AMGEVITA is being developed as a biosimilar candidate to Humira (adalimumab). The proposed indications for AMGEVITA are those approved for Humira.

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 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 disease-modifying anti-rheumatic drugs (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 disease-modifying anti-rheumatic drug 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 adult patients with an inadequate response to conventional systemic HS therapy.

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, a corticosteroid, and 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.

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

About the product

AMGEVITA (ABP 501) is being developed as a biosimilar candidate to Humira (adalimumab). ABP 501 is a fully human immunoglobulin G1 monoclonal antibody which binds and neutralizes human tumor necrosis factor alpha (TNFα), a cytokine which mediates the inflammatory response. The amino acid sequence of ABP 501 is identical to that of the reference product, adalimumab. The ABP 501 and adalimumab active ingredients are manufactured using recombinant DNA technology in Chinese hamster ovary cells. ABP 501 has the same dosage form and strength as adalimumab.

By binding TNFα and preventing its interaction with its receptors, tumor necrosis factor receptor superfamily (TNFRSF) 1A (p55) and TNFRSF1B (p75), adalimumab interferes with downstream signaling and thereby suppresses immune processes central to several chronic inflammatory diseases. Based on extensive similarity data presented herein, ABP 501 is expected to have a safety and efficacy profile similar to that of adalimumab in all indications approved for adalimumab. Thus, the proposed indications for ABP 501 are based on those currently approved for adalimumab.

Type of Application and aspects on development

This Marketing Authorisation Application is an abridged application for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

Similarity is claimed to Humira (adalimumab) as the reference medicinal product, which has been marketed in the European Union for over 10 years. Humira 40 mg solution for injection in a prefilled syringe was first authorised in the EU on 8 September 2003; the Marketing Authorisation Holder is AbbVie Ltd.

ABP 501 is a recombinant human IgG1 monoclonal antibody with an identical amino acid sequence to that of adalimumab.

Two Scientific advices were obtained; the first one in November 2011 (EMEA/H/SA/2216/1/2011/111) and a follow-up to the advice provided by CHMP was obtained in October 2012 (EMEA/H/SA/2216/1/FU/1/2012/III), with questions concerning quality, pre-clinical and clinical development:

CHMP stated that a pivotal study based on 52 weeks on Ps population could be acceptable. However, the CHMP considered the PS study as not sufficient as standalone to support biosimilarity and it would have preferred to have the 12 month data from the RA study as pivotal or in support of Ps data. Moreover, the preferred primary endpoints by CHMP were PASI variable analyzed as a continuous outcome in Ps study and ACR20 in RA study.

The MAA is based on a 52 weeks study on Ps in which the primary endpoint is PASI percent improvement at week 16 and on a 6 months RA study in which the primary endpoint is ACR20.

Advice was also given on the adequacy of analytical and pharmacological comparability between ABP-501 and Humira, including possible differences in structural characteristics along with in vitro studies (potency assay, FcRn Binding, FcyRIIIa, ADCC- and CDC activity) and ex-vivo pharmacological tests, which were selected to evaluate the binding, neutralizing, specificity and effector functionality of ABP 501. Among the in vitro studies submitted by the Applicant, binding to FcyRs isoforms FcyRIIB and FcyRIIIB as well as binding to complement (Cq1) were not taken into consideration.

2.2. Quality aspects

2.2.1. Introduction

AMGEVITA, referred to as ABP 501, has been developed as a biosimilar candidate to Humira (adalimumab). ABP 501 is a fully human monoclonal immunoglobulin IgG1 that specifically binds to human tumor necrosis factor α (TNF-α) and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leucocyte migration (ELAM-1, VCAM-1, and ICAM-1).

ABP 501 also binds Fcγ receptors (FcγRs) and induces both antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) *in vitro*.

The amino acid sequence of ABP 501 is identical to that of the reference product, adalimumab. The ABP 501 and adalimumab active ingredients are manufactured using recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. ABP 501 has the same dosage form and strength as adalimumab.

AMGEVITA is presented as solution for subcutaneous injection and two strengths are proposed:

- 20 mg in a single-dose pre-filled syringe (PFS), each containing 20 mg of adalimumab in 0.4 mL (50 mg/mL) solution;

- 40 mg in a single-dose pre-filled syringe or single-dose pre-filled pen (PFP) (SureClick, each containing 40 mg of adalimumab in 0.8 mL (50 mg/mL) solution.

Adalimumab is formulated with glacial acetic acid, sucrose, polysorbate 80, sodium hydroxide and water for injections.

2.2.2. Active Substance

General information

ABP 501 is a fully human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass expressed in the CHO cell line and consists of 2 heavy chains (HC), and 2 light chains (LC) of the kappa subclass. ABP 501 contains 32 total cysteine residues involved in both intrachain and interchain disulfide bonds. Each HC contains 451 amino acids with 4 intrachain disulfides. Each LC contains 214 amino acids with 2 intrachain disulfides. Each HC contains an N-linked glycan at the consensus glycosylation site on Asn301. As is typical with mammalian cell culture processes, the HC C-terminal Lys451 is mostly removed due to the presence of carboxypeptidases during the cell culture process.

The molecular formula for the predominant ABP 501 HC isoform (C-terminal glycine) is C2191H3392N582O677S15, not including N-linked glycans. The molecular formula for ABP 501 LC is C1027H1610N282O332S6. The theoretical mass of fully assembled, disulfide-bonded ABP 501 antibody with HC C-terminal glycine and without the addition of the N-linked glycans is 145,192 Da. The predominant glycan moiety, A2G0F, has an empirical formula of C56H92N4O39 and has an empirical mass of 1,445 Da. Thus, the theoretical mass of glycosylated ABP 501 containing 2 N-linked glycans (1 per heavy chain) is 148,081 Da. The experimentally determined predominant ABP 501 mass is 148,083 Da, in agreement with the theoretical value.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Amgen Thousand Oaks (ATO), USA, is responsible for active substance manufacture.
The ABP 501 clonal production cell line was generated at Amgen. The ABP 501 amino acid sequence was derived from a commercial lot of Humira (adalimumab). The deduced DNA sequence was synthesised for the heavy chain (HC) and light chain (LC) variable regions, and the variable region DNA was used to construct the ABP 501 HC and LC expression plasmids in a stepwise manner.

The host cell line used for expression of ABP 501 is a serum-free CHO cell line. This cell line was derived by gradually adapting the CHO cell line to grow in serum-free medium.

The HC and LC expression plasmids were co-transfected into CHO cells. Following a clone screening and selection process, final clone 11-1-300-23 was selected as the ABP 501 production cell line.

A two-tiered cell banking system consisting of a master cell bank (MCB) and a working cell bank (WCB) was established. The cell banks were characterised in accordance with ICH guidelines.

A single production lot is initiated from a single WCB vial thaw. The manufacturing process for the active substance includes steps for cell culture, harvest, purification with a series of chromatography, viral inactivation/filtration and ultra-/diafiltration steps.

The container closure system for drug substance is a 10 L polycarbonate container with a polypropylene screw thread cap and thermoplastic elastomer gasket.

Reprocessing is not currently proposed during manufacturing of ABP 501 active substance.

In-process controls (IPCs) are used to monitor the manufacturing process to ensure that the active substance and resulting finished product will meet quality requirements, or to monitor process consistency. IPCs are part of the control strategy. Justification of the IPC limits is provided.

Control of materials

a) Control of source and starting materials of biological origin:

The Applicant's viral safety program minimises the potential for introduction of adventitious virus into the ABP 501 manufacturing process through contaminated raw material and includes the following:
- MCB and WCB have been extensively tested and found to be free of detectable adventitious agents;
- Raw materials have appropriate certification, and no animal derived materials are used in the manufacturing process.

An assessment of risk for transmissible spongiform encephalopathy (TSE) transmission was performed on all raw materials from transfection of the cell line through fill and finish of the finished product. Materials not directly used in the process, but which may come into contact with the product during manufacturing or primary packaging, were also identified and assessed.

Based on the complementary strategies of the viral safety program and adventitious agents safety evaluation results, Amgen concludes that the viral risk and TSE risk associated with this product are negligible.

b) Raw materials:

All manufacturing raw materials are received, identified, sampled, quarantined, tested, labeled, and released according to established written procedures. A listing of raw materials and process solutions, including cell culture media, stock solutions and buffers, used in the ABP 501 active substance manufacturing process was provided. Compendial materials are tested to the referenced compendia. Specifications are provided for all non-compendial materials and media solutions used in the process.

c) Source, history and generation of cell substrate:

The ABP 501 clonal production cell line was generated at Amgen. The source, history and generation of the cell substrate and cell line development was described.

d) Genetic stability of the production cell line:

The genetic stability for ABP 501 production has been assessed from thaw of the MCB through creation of the WCB to the end of production (EOP) for a typical active substance lot and also through the EOP to the limit of *in vitro* cell age (LIVCA) for manufacturing.

The LIVCA was determined by extending the population doublings from a typical EOP run during ABP 501 manufacture at the commercial site and scale. The culture age is controlled to less than the LIVCA in the commercial manufacturing process through operational controls.

Lot release data for the active substance generated from the LIVCA production culture confirmed that product quality at the defined LIVCA is consistent with results for other lots produced with lower population doubling levels.

The results for the molecular characterisation of the integrated HC and LC genes demonstrate that the ABP 501 cell line is stable throughout the production process to the currently established LIVCA.

Process validation

The active substance manufacturing process was validated. Validation acceptance criteria for process parameters and performance indicators were based on reference product data, process understanding gained from prior knowledge, process characterisation and clinical manufacturing. Process validation was completed for cell culture, harvest, purification and in-process pool holds. Validation data demonstrate that the process is controlled and reproducible while consistently producing active substance having the required quality when conducted within the defined operating ranges.

Manufacturing process development

Minor changes to controls and processing conditions were implemented during development to ensure process robustness. Product quality assessments have demonstrated that the active substance produced throughout development is comparable.

Characterisation

Elucidation of structure

All elucidation of structure studies were conducted on an ABP 501 active substance lot.
ABP 501 was characterised to provide a comprehensive understanding of its structural and functional properties and to support an assessment of criticality of product quality attributes (PQAs). ABP 501 characterisation included the following studies:

- Biochemical studies to assess primary structure, glycosylation, disulfide structure, charge variants, and size variants;
- Biophysical studies to assess secondary structure, tertiary structure, and thermal stability;
- Biological studies to demonstrate the mechanism of action, including antigen specificity and Fc functionality;
- Forced degradation studies to assess how ABP 501 responds to specific stress conditions to reveal potential degradation pathways under typical and atypical conditions and further understand PQAs.

The *in vitro* biological activity of ABP 501 was studied using recombinant protein and cell-based binding and functional assays, assessing both antigen-specific functions and Fc-mediated functions. The characterisation methods were intended to assess (1) antigen binding, (2) potency with respect to the primary mechanism of action, and (3) Fc functionality.

ABP 501 exerts its effects in autoimmune diseases primarily via binding to soluble TNF-α (sTNF-α) and the membrane-bound precursor form, transmembrane TNF-α (mbTNF-α). Additionally, ABP 501 binds neonatal Fc receptor (FcRn) and Fc gamma receptors (FcγR) and mediates effector functions such as ADCC) and CDC *in vitro*.

ABP 501 binds human and non-human primate TNF-α with high affinity, but does not bind human lymphotoxin alpha (LTα).

Impurities

Based on comprehensive characterisation of ABP 501, the product-related impurities were identified. The product-related impurities were determined to have a potential impact on patient safety or product efficacy. The product-related impurities present are present at very low levels in the active substance and are controlled to acceptable levels by the manufacturing process. The risk assessment and overall control strategy for each of these product-related impurities was presented.

Process-related impurities encompass those derived from or introduced during the active substance manufacturing process. Included are impurities from the host cell line and raw materials used during cell culture and downstream processing.

The removal of host cell proteins (HCP), DNA, and residual protein A in the active substance process was evaluated in commercial-scale runs. Removal of these impurities to predefined acceptance criteria

was demonstrated during challenge studies performed at small-scale during process characterisation and confirmed during process validation.

Specification

The active substance specification covers identity, purity, potency, adventitious agents and general tests.

During the development of ABP 501, a number of analytical procedures were included on the clinical active substance specification that have been either removed from the specification due to additional product and process understanding and demonstrated process performance, or moved to in-process testing due to the presence of redundant testing points.

The dataset used to calculate and establish the acceptance limits included release testing results from the active substance, as well as stability data from active substance lots held at the recommended storage conditions. Considerations for establishing the specification acceptance criteria also included:

- Process and product characterisation data;
- Manufacturing experience with similar monoclonal antibody processes;
- Formulation development studies;
- Analytical method performance;
- Acceptable safety levels;
- World Health Organization (WHO), United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.) and International Conference on Harmonization (ICH) guidelines.

Active substance lot release results with numerical limits are routinely tracked as part of a data monitoring program. The monitoring program establishes statistically derived control limits per internal procedures that are more stringent than the lot release and stability acceptance limits. This additional control provides early visibility to potentially adverse product quality trends that may be observed during manufacturing and/or stability and ensures a timely response and quality investigations. This program helps to ensure that all active substance lots will meet the expected quality profile and specified acceptance limits during release testing and throughout the shelf life.

Batch analysis

Batch analyses data were provided for all ABP 501 active substance lots used during development through process validation. A comparison of product quality results between clinical and commercial active substance lots was provided.

Reference material

A primary reference standard has been used for lot release testing of all active substance and finished product lots manufactured to date and used for the analytical similarity assessment. The primary reference standard will be used to qualify future reference standards which will be created, as needed, to ensure sufficient supply for release and stability testing. The primary reference standard was qualified.

Stability

Based on stability data collected to date, an expiry period is supported for ABP 501 active substance stored at the recommended storage temperature. Stability studies were conducted at the recommended storage temperature to support the expiry period. The long-term stability studies were performed according to ICH Q5C guideline.

Stability data at the accelerated storage conditions demonstrate the active substance remains stable under accelerated conditions. Stability data at the stressed storage condition demonstrate that the active substance remains stable under stressed conditions.

2.2.3. Finished Medicinal Product

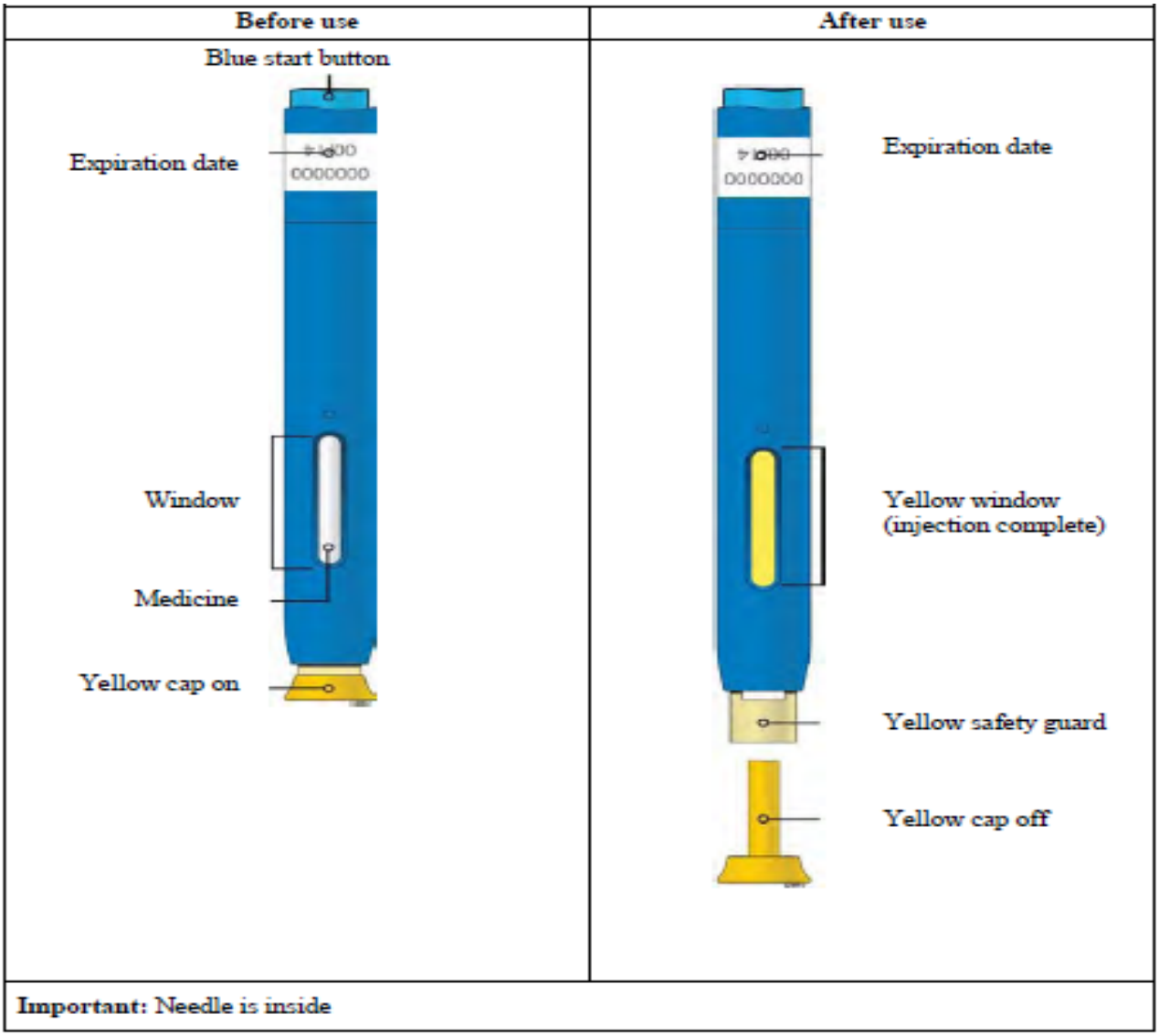
Description of the product and pharmaceutical development

The ABP 501 finished product is supplied as a sterile, single-use, preservative-free solution for subcutaneous injection in either a PFS or a single-use, disposable, hand-held, mechanical (spring based) pre-assembled PFP auto-injector SureClick.

ABP 501 is formulated with glacial acetic acid, sucrose, polysorbate 80, sodium hydroxide quantum sufficient to target pH 5.2 and water for injections.

The nature and contents of container consist of:
- 0.4 mL or 0.8 mL solution in PFS (type I glass) with a plunger stopper (bromobutyl rubber) and a stainless steel needle (27-gauge [27G] or 29-gauge [29G]) with a needle shield (thermoplastic elastomer).
- 0.8 mL solution for injection in PFP for patient use containing a PFS (type I glass). The pen is a single use, disposable, handheld, mechanical injection device.
The needle cover of the PFS and PFP is made from dry natural rubber (a derivative of latex).

Figure 1– AMGEVITA pre-filled pen – guide to parts



The active substance and finished product have an identical formulation. The formulation is not modified during finished product manufacturing.

The excipients were chosen to ensure active substance and finished product stability. Active substance and finished product stability data confirm the compatibility of ABP 501 with the excipients. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

There are no formula overages in ABP 501 finished product. Syringes are filled to ensure that there is a sufficient deliverable volume provided from each syringe.

Manufacture of the product and process controls

The finished product has the same formulation and concentration as the active substance. Therefore, no dilution is required for finished product manufacturing and the concentrations of active and excipients remain the same.

Reprocessing is not currently proposed during manufacturing of ABP 501 finished product.
IPCs are used to ensure process consistency and product quality during the manufacture of the PFS. The critical IPCs for the finished product manufacturing process are included in the process flow diagram of the finished product manufacturing process.

Manufacturing controls have been established to ensure appropriate assembly of the auto-injector. The assembly process has been demonstrated to have no adverse impact to product quality.

The ABP 501 finished product process validation strategy was designed to demonstrate that the manufacturing process is controlled and reproducible, consistently yielding finished product with the required product quality.

Product specification

The finished product release specification includes identity, purity, potency and other general tests.

Batch analyses

Batch analyses data were provided for all ABP 501 finished product lots using during development through process validation.

Stability of the product

Based on stability data collected to date, in accordance with ICH Q5C guideline, a shelf life of 24 months is acceptable for the finished product stored at the recommended storage condition of 2°C to 8°C. Additionally, to enhance convenience and facilitate dosing, storage for 14 days up to 25°C is proposed and accepted.

Stability studies conducted at accelerated storage conditions (25°C and 30°C) demonstrated that the finished product remains stable under accelerated conditions for 1 month. Stability data at the stressed storage conditions (40°C) demonstrated that the finished product remains stable at the stressed conditions for 1 week.

Stability of the finished product after exposure to light, temperature cycling, typical transport conditions, and room temperature at end of shelf life have also been evaluated. Results of these studies, together with results from the accelerated and stressed stability studies, demonstrate that the finished product is stable in the primary container, protected from light, under conditions that may be encountered during transport, storage, handling, and use. Results have also been presented demonstrating that the secondary packaging effectively protects the finished product from light exposure.

Adventitious agents

Non-viral Adventitious Agents

The ABP 501 manufacturing process incorporates control measures to prevent contamination and maintain microbial control.

An assessment of risk for TSE transmission was performed on all raw materials used to produce ABP 501, from the transfection of the cell line through fill and finish of the finished product.
The ABP 501 manufacturing process does not use excipients, cell culture media components, or purification resins of animal origin.

In addition, materials not directly used in the process, but which may come into contact with the product during manufacture or primary packaging, were identified and assessed for BSE/TSE transmission risk. For those materials manufactured using animal tallow derivatives, the processing conditions meet the "rigorous processes" criteria defined in EMA 410/01 TSE guideline.
It is considered that the TSE risk associated with ABP 501 is negligible.

Viral Adventitious Agents

Adventitious Agents Testing of Cell banks

The MCB, WCB and cells at the limit of *in vitro* cell age (LIVCA) have been tested as recommended in the relevant ICH guideline. Testing results confirmed that the cell banks are sterile and free of detectable mycoplasma or viruses, with the exception of expected A-type and C-type retrovirus-like particles (RVLP). No bovine or porcine viruses were detected in any of the cell banks tested.

Process Viral Clearance Assessment

Five steps of the ABP 501 manufacturing process were evaluated for their ability to remove or inactivate model viruses

Viral validation studies were carried out in accordance with ICH Q5A guideline.
Where applicable, the evaluated steps were scaled down from the commercial purification process. Scale-down included the use of process intermediates obtained from development or clinical batches manufactured by the intended commercial process and scale. Process buffers and solutions were prepared in accordance with the commercial process. In addition, processing conditions were maintained between scales.

Comparisons of the relevant process parameters and performance indicators between small-scale model and commercial process have been provided in tabular format. The results presented indicate that performance was comparable to the commercial-scale production runs.
The chromatography steps were evaluated with both new and used (cycled) resins to demonstrate that the viral clearance capacity does not change for a given column over the lifetime of the resin. Used resins were generated during the execution of small-scale chromatography lifetime studies. Upon completion of the resin lifetime studies, used resins (were re-slurried and packed into individual columns for the virus challenge studies for comparison to new resin.

Four model viruses were used in viral validation studies.

Comparability exercise for the finished medicinal product

ABP 501 has been developed as a biosimilar product to the reference product Humira (adalimumab [EU]) (EMEA/H/C/000481). The Applicant performed a comprehensive analytical similarity assessment using state-of-the-art methods and has determined that:
- ABP 501 is analytically similar to the reference product;
- ABP 501 has the same primary amino acid sequence as the reference product;
- ABP 501 has the same strength as the reference product.

The ABP 501 clinical program includes 3 studies to support the application (Table 1). Amgen used both US-sourced Humira (adalimumab [US]) (BLA 125057) and EU-sourced Humira (adalimumab [EU]) in the clinical program.

Table 1 – ABP 501 clinical studies

Study Number	Subject Population	Type	Investigational Products
20110217	Healthy subjects	PK similarity, safety, tolerability, immunogenicity	ABP 501, adalimumab (US), adalimumab (EU)
20120262	Rheumatoid arthritis	Efficacy, safety, immunogenicity	ABP 501, adalimumab (US)
20120263	Plaque psoriasis	Efficacy, safety, immunogenicity	ABP 501, adalimumab (EU)

PK = pharmacokinetic

To support the use of clinical data generated using adalimumab sourced from both regions, Amgen has established a scientific bridge between adalimumab (US) and adalimumab (EU), which is based on 3-pair wise analytical and PK comparisons. To complete the analytical comparisons, all 3 products were subjected to the same testing plan. Thus, the analytical similarity assessment consists of 3-pair wise comparisons (Table 2).

Table 2 – Definitions for analytical similarity pair-wise comparisons

Comparison	Purpose	Test Product	Reference Product
ABP 501 vs adalimumab (EU)	Similarity	ABP 501	adalimumab (EU)
ABP 501 vs adalimumab (US)	Reference bridging	ABP 501	adalimumab (US)
adalimumab (US) vs. adalimumab (EU)	Reference bridging	adalimumab (US)	adalimumab (EU)

The methods used for the analytical similarity assessment were selected based on knowledge regarding the structure, function, and heterogeneity of the reference product and ABP 501, including those characteristics critical to the biological activity and stability of the product. The Applicant performed a comprehensive analytical similarity assessment which included comparative evaluations of biological activities, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, thermal stability and degradation studies, general properties, and process-related impurities. The methods were validated or qualified and deemed suitable for their intended use.

To inform analytical similarity assessment, data for similarity assays/attributes that have the potential to impact clinical outcomes were evaluated against similarity assessment criteria. In instances where the data did not meet the assessment criteria, the differences were justified with regards to its potential to impact clinical outcomes.

The results demonstrate that:

- ABP 501 has similar biological activity compared to the reference product.
- ABP 501 has the same amino acid sequence and similar structure compared to the reference product.
- ABP 501 has similar strength compared to the reference product.

- ABP 501 has a similar glycan map profile compared to the reference product, with minor quantitative differences. These minor differences are not considered meaningful.
- ABP 501 has a similar profile for size variants compared to the reference product.
- ABP 501 has a similar profile for charge variants compared to the reference product.
- ABP 501 has a similar particle profile compared to the reference product.
- ABP 501 has a similar thermal degradation profile compared to the reference product.
- ABP 501 has similar general properties compared to the reference products.
- ABP 501 does not have any significant differences in process-related impurities compared to the reference product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

The information requested to support adequate control of viral safety has been provided, the characterisation for qualification of the MCB, WCB and end-of-production (EOP) cells is concluded acceptable.

The descriptions of the different manufacturing steps are considered acceptable. As requested, supplementary documentation has been provided supporting adequate control of elution of product from the chromatography steps. As previously requested, the Applicant also confirmed that operation of any of the critical process parameters (CPPs) outside the defined acceptable range will trigger the same investigations as is described for action limits controlling IPC tests.

An acceptable justification has been provided for not including analyses of the primary and higher order structures in the studies conducted supporting comparability of active substance before and after introduction of optimised control of the production bioreactor step.

In primary assessment, the proposed integrated control strategy was considered insufficient to assure that the commercial active substance is of the appropriate quality (Major Objection). Indeed, control strategy as initially proposed seemed to allow a large degree of process flexibility without an adequate testing of relevant product quality attributes at release (or in-process) to assure consistency of commercial lots. Comprehensive supportive documentation has been provided in the Applicant's response, including for example the introduction of new IPC tests as well as the tightening of action limits/specifications for tests applied for in process and release control of relevant product quality attributes to assure consistency of commercial lots. The overall control strategy applied in production is considered satisfactorily supported.

The specification for control of active substance is only limited. However, in-process tests for control of purity are indicated at different steps in the downstream process. Their designation as IPC tests in production of active substance is considered acceptable as the same tests are controlled by specifications for finished product. The action/rejection criteria proposed for these tests were however considered to be set too wide but were tightened to ensure that the finished product will comply with the end-of-shelf-life specifications.

Similarly, tests for control of general properties are indicated as IPC tests. As the Applicant has agreed to follow the recommendations given in the primary assessment on the control of these parameters on the level of finished product, this is considered acceptable.

The upper limit proposed for specification hat were considered to be set too wide to assure that the ADCC activity of commercial ABP501 finished product will remain within the range that has been shown to be safe and efficacious has now been tightened and acceptably justified.

Taken together, the stability data included in the primary submission and submitted response, are considered acceptable to support the proposed shelf life for active substance of 48 months, when stored at the recommended storage temperature.

Finished product

Relevant tests are included in the release specification for the finished product. The specification was revised in accordance with CHMP request.

Updated stability data were provided during the review, including up to 36 months data from primary and supportive stability lots in the statistical evaluation of data, giving satisfactory support that finished product remains within the proposed stability specification. The statistical evaluation of the extended stability data was conducted in line with the recommendations in the ICH Q1E guideline.

As requested, the Applicant re-evaluated and tightened the finished product end-of-shelf-life-specification for acidic species in order to assure that acidic species remain within the range that can be considered clinically qualified. In relation to this issue, the Applicant also reduced the shelf life from 36 to 24 months. This is acceptable

The maximum of 14 days hold time at up to 25°C and protected from light, within the 24 months shelf life of the finished product, is acceptable as the worst case conditions tested give enough assurance of the requested stability.

The information provided regarding adventitious agents safety has been revised in accordance with the request by CHMP and is considered acceptable.

Biosimilarity exercise

The design of the biosimilarity studies is considered acceptable, including with a few exceptions relevant analytical methods for assessment of comparability in the structure, function and heterogeneity of ABP 501 and reference product. The concerns raised on whether the ADCC and CDC bioassays where sufficiently sensitive to detect differences related to variability in the levels of high mannose and the galactosylation profile, have been satisfactorily addressed, showing adequate performance of both analytical procedures.

In most aspects, the approaches used for establishment of the biosimilarity assessment criteria are considered acceptable. However, no discussion or justification was presented supporting the proposed definition of acceptance criteria for statistical evaluation of data. According to the proposed criteria, conclusion on comparability will be made if > 90 % of individual batches of biosimilar product fall within the calculated range of mean + 3 Standard Deviations (SD) for reference product, which leads to acceptance of a too wide range in product quality. However, as data from the analysis of individual batches are provided for all analyses where results have been statistically evaluated, assessment can be made independent of the statistical model used.

For assays/attributes where a change over time is observed when stored at the recommended storage condition, all values were adjusted for material age prior to computing the quality range. Even though this approach was considered theoretically sound, it was pointed out that this could introduce a bias instead of a correct age-adjustment. The Applicant gave satisfactory reassurance of the reliability of the comparison of data.

The ABP 501 product batches included in the biosimilarity assessment were not considered representative for commercial production, as the proposed specifications opened for a considerably wider range in quality of commercial finished product than those studied in the comparative analysis. In response to the raised concern, the specifications for control finished product purity have been tightened. The limits have now been satisfactorily revised and justified.

Taken together, the data presented is considered acceptable to show that there are no significant qualitative or quantitative differences between reference and biosimilar product at end of storage besides those that can be attributed to differences in the levels of C-terminal lysine.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of AMGEVITA is considered to be in line with the quality of other monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

Biosimilarity with the reference medicinal product Humira has been sufficiently demonstrated. From a quality point of view, the observed differences and levels of these differences have been well documented and are acceptable.

The overall quality of AMGEVITA is considered acceptable.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical program is in line with the recommendations in the *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues* (EMA/CHMP/BMWP/403543/2010). For some aspects (in vivo toxicology studies in cynomolgus monkeys), the program goes beyond these recommendations, but these studies were primarily conducted in order to fulfil requirements in other regions. The toxicology and toxicokinetics studies in cynomolgus monkeys were conducted in accordance with GLP.

In a CHMP Scientific Advice, given in 2011, an outline of the *in vitro* biological assay strategy was generally agreed.

The nonclinical program was designed to assess pharmacological activity, PK, and toxicological characteristics of ABP 501 as part of the stepwise assessment of similarity. To support a “global” development programme, an analytical comparability exercise was performed by Amgen on batches of “adalimumab (US) and “adalimumab (EU)”, approach considered acceptable by EMA (Scientific Advice EMA/CHMP/SAWP/868010/2011, procedure no EMEA/H/SA/2216/1/2011/III), provided that a sufficient number of EU reference product batches were included. Advice was given on the adequacy of analytical and pharmacological comparability between ABP-501 and Humira, including possible differences in structural characteristics along with in vitro studies (potency assay, FcRn Binding, FcyRIIIa, ADCC- and CDC activity) and ex-vivo pharmacological tests selected to evaluate the binding, neutralizing, specificity and effector functionality of ABP 501. The SA also dealt with the non-clinical PK and Toxicology program consisting of a 4-week non-human primate toxicology study, which was designed in order to fulfil US-FDA requirements and therefore designed to examine the differences in formulation between Humira (US) and ABP 501. Although it was submitted by the Applicant in the present MAA, such a study is not required for marketing authorization in the EU.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary Functional Assays for Potency

For the biosimilarity evaluation, a number of *in vitro* pharmacological assays have been performed where ABP 501 has been compared to commercially available adalimumab (Humira) from both EU and US. A limited number of methods have been selected for more extensive comparisons:

- Inhibition of sTNFα-induced apoptosis in U937 cells
- Binding to sTNFα
- Binding to FcγRIIIa(158V)
- Binding to FcRn
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Complement-dependent cytotoxicity (CDC)

These evaluations have been performed with assays that are expected to show a good ability to detect differences of possible clinical relevance, and have been performed with a large number of lots of each product (≥10) in order to address variability. See Quality section of the report for a full assessment of these data. The results from the above mentioned studies are considered as the pivotal data set for the similarity evaluation.

Additional characterization assays

An overview of the Primary PD studies is provided in the Table below.

Table 1- Primary pharmacodynamic studies

<table>
<tr><th>Study report</th><th>Test System</th><th>Method / test article batches</th><th>Results</th></tr>
<tr><td colspan="4">Binding to TNFα</td></tr>
<tr><td>Study R20120006

Affinity of ABP 501 and Adalimumab (EU- and US-sourced) to human and cynomolgus monkey TNFα</td><td>In vitro soluble, recombinant human TNF α protein (cat#300-01A lot#0302CY25)

and NHP TNFα Protein (cat#1070-RM lot#FXU0610021)</td><td>Surface Plasmon Resonance (SPR) analysis

ABP 501 Drug Product material, lots #0010085289, #0010085295, #0010085297

Adalimumab (US)

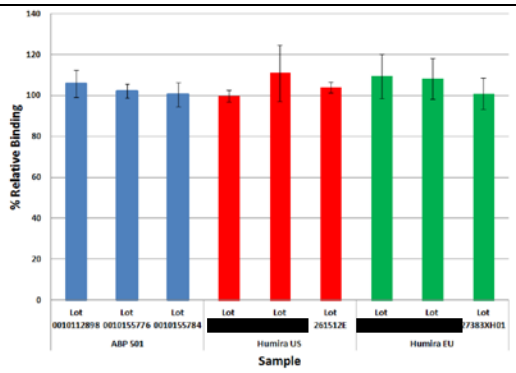
Adalimumab (EU)</td><td>
Table 2. Comparative Binding Affinity of ABP 501, Adalimumab (US), and Adalimumab (EU) to Human TNFα by Biacore Single Cycle Kinetics
<table>
<tr><th>Experiment</th><th>Sample</th><th>On Rate k_a (1/Ms)</th><th>Off Rate k_d (1/s)</th><th>Equilibrium K_d (pM)</th></tr>
<tr><td>1</td><td>ABP 501 Lot 0010085289</td><td>7.62 E + 5</td><td>3.94 E - 5</td><td>52</td></tr>
<tr><td></td><td>Adalimumab (US) [redacted]</td><td>7.45 E + 5</td><td>3.94 E - 5</td><td>53</td></tr>
<tr><td></td><td>Adalimumab (EU) Lot 92081XD01</td><td>8.08 E + 5</td><td>4.38 E - 5</td><td>54</td></tr>
<tr><td>2</td><td>ABP 501 Lot 0010085295</td><td>7.69 E + 5</td><td>3.73 E - 5</td><td>48</td></tr>
<tr><td></td><td>Adalimumab (US) [redacted]</td><td>8.34 E + 5</td><td>3.98 E - 5</td><td>48</td></tr>
<tr><td></td><td>Adalimumab (EU) Lot 02129XH14</td><td>8.58 E + 5</td><td>3.90 E - 5</td><td>46</td></tr>
<tr><td>3</td><td>ABP 501 Lot 0010085297</td><td>8.35 E + 5</td><td>4.28 E - 5</td><td>51</td></tr>
<tr><td></td><td>Adalimumab (US) [redacted]</td><td>8.12 E + 5</td><td>4.27 E - 5</td><td>53</td></tr>
<tr><td></td><td>Adalimumab (EU) Lot 07182XD03</td><td>8.65 E + 5</td><td>4.44 E - 5</td><td>51</td></tr>
</table>
adalimumab (EU) = Humira®, which is approved and marketed in the European Union; adalimumab (US) = Humira®, which is approved and marketed in the United States; k_a = association rate constant; k_d = dissociation rate constant; K_d = dissociation equilibrium binding constant; TNFα = tumor necrosis factor alpha

Table 3. Comparative Binding Affinity of ABP 501, Adalimumab (US), and Adalimumab (EU) to Cynomolgus Monkey TNFα by Biacore Single Cycle Kinetics
<table>
<tr><th>Experiment</th><th>Sample</th><th>On Rate k_a (1/Ms)</th><th>Off Rate k_d (1/s)</th><th>Equilibrium K_d (pM)</th></tr>
<tr><td>1</td><td>ABP 501 Lot 0010085289</td><td>5.04 E + 5</td><td>3.96 E - 5</td><td>79</td></tr>
<tr><td></td><td>Adalimumab (US) [redacted]</td><td>4.81 E + 5</td><td>4.00 E - 5</td><td>83</td></tr>
<tr><td></td><td>Adalimumab (EU) Lot 92081XD01</td><td>5.21 E + 5</td><td>4.37 E - 5</td><td>84</td></tr>
<tr><td>2</td><td>ABP 501 Lot 0010085295</td><td>6.25 E + 5</td><td>4.06 E - 5</td><td>65</td></tr>
<tr><td></td><td>Adalimumab (US) [redacted]</td><td>6.07 E + 5</td><td>3.87 E - 5</td><td>64</td></tr>
<tr><td></td><td>Adalimumab (EU) Lot 02129XH14</td><td>6.41 E + 5</td><td>4.14 E - 5</td><td>65</td></tr>
<tr><td>3</td><td>ABP 501 Lot 0010085297</td><td>5.66 E + 5</td><td>3.60 E - 5</td><td>64</td></tr>
<tr><td></td><td>Adalimumab (US) [redacted]</td><td>5.56 E + 5</td><td>3.51 E - 5</td><td>63</td></tr>
<tr><td></td><td>Adalimumab (EU) Lot 07182XD03</td><td>5.85 E + 5</td><td>3.82 E - 5</td><td>65</td></tr>
</table>
adalimumab (EU) = Humira®, which is approved and marketed in the European Union; adalimumab (US) = Humira®, which is approved and marketed in the United States; k_a = association rate constant; k_d = dissociation rate constant; K_d = dissociation equilibrium binding constant; TNFα = tumor necrosis factor alpha.
</td></tr>
<tr><td>Study R20140020

Binding to membrane-associated TNFα</td><td>CHO cells over-expressing membrane-bound huTNFα</td><td>In vitro competition binding assay

ABP 501 DP Lot 0010112898 , ABP 501 DP Lot0010155776, ABP 501 DP Lot 0010155784

Adalimumab (US)

Adalimumab (EU)</td><td>


** The relative binding values were calculated with respect to the ABP 501 reference standardLot 0010085289.
</td></tr>
<tr><td colspan="4">Neutralization of Human TNFα-induced Signaling</td></tr>
<tr><td>Study R20120007

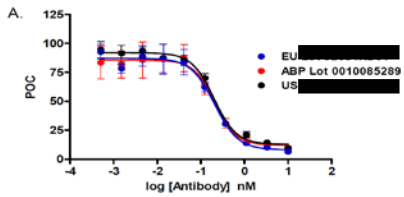
Comparative Neutralization of Human TNFα and Specificity against LTα Induced Signaling in HUVEC by ABP 501</td><td>Recombinant human TNFα (cat#300-01A lot#0302CY25)

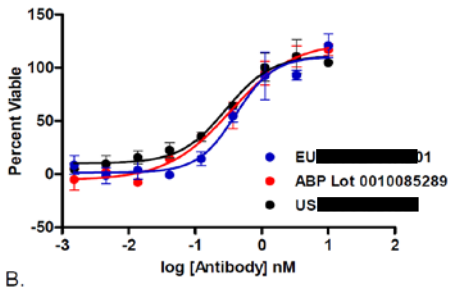
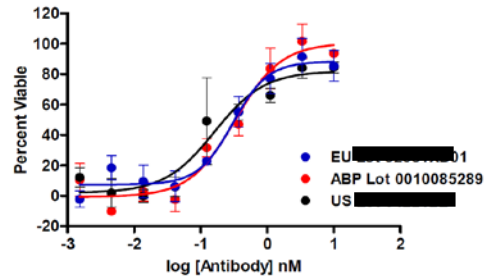
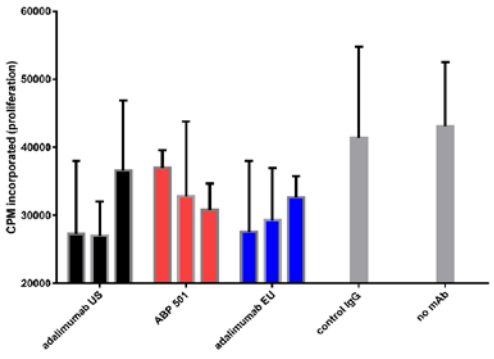
Recombinant human LTα (cat#211-TB lot#AB3209031)

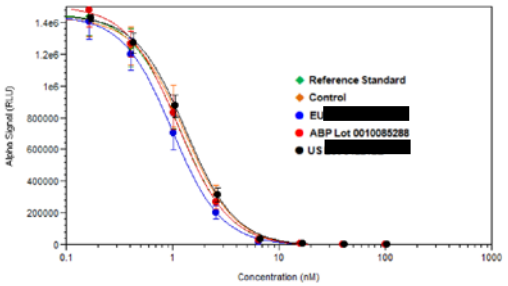
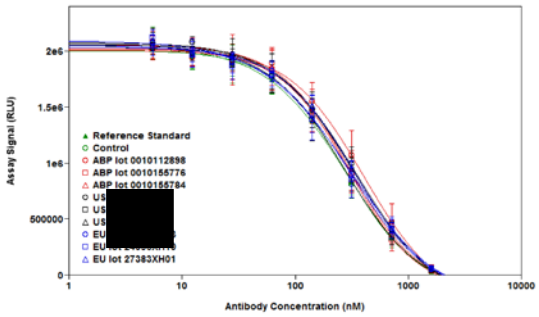
HUVEC cells (cat#CC-517)</td><td>Immunoassay

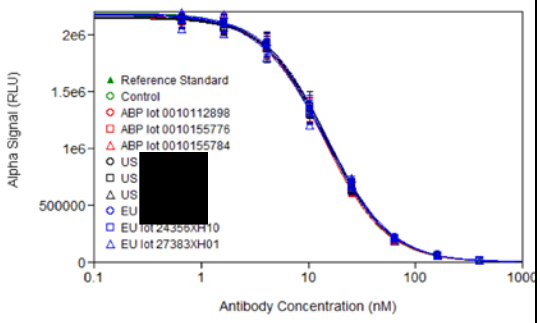
ABP 501 Drug product batch 0010085289 Adalimumab (EU)

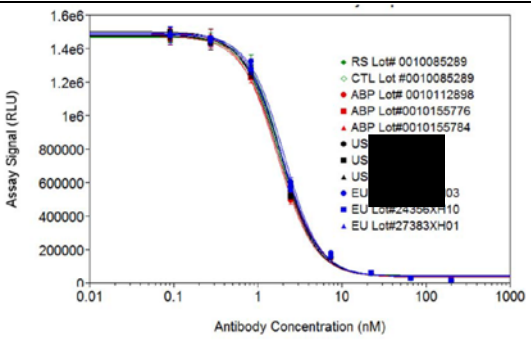
Adalimumab (US)</td><td></td></tr>
</table>

			 (A) = inhibition of TNFα-induced IL-8 (B) = inhibition of LTα-induced IL-8
Study R20120150 Neutralization of Human TNF alpha-induced Signaling In HUVEC by Multiple Lots of ASP 501 and Adalimumab Inhibition of TNFα-induced IL-8 secretion by multiple lots of ABP 501, adalimumab (US), and adalimumab (EU) in HUVEC.	Recombinant human TNFα (cat no. 300-01A, lot no. 0302CY25), EBM-2 (cat no. CC-3156) and EGM-2 bullet kit (cat no. CC-3162) MA6000 Human IL-8 tissue culture kit (cat no. K111ANB-2) HUVEC cells (cat no. CC-2517)	Immunoassay ABP 501 Drug Product material, lots 0010085289, 0010085295, and 0010085297 Adalimumab (US) Adalimumab (EU)	**ABP 501** EC_{50} values for inhibition of TNFα-induced IL-8: 204 pM, 294 pM, and 200 pM for the 3 lots tested. **Adalimumab (US)** EC_{50} values: 171 pM, 156 pM, and 166 pM for the 3 lots tested. **Adalimumab (EU)** EC_{50} values: 177 pM, 168 pM, and 222 pM for the 3 lots tested.
Neutralization of TNFα-induced cell death			
Study R20120008 Neutralization of Human and Nonhuman Primate TNFa-induced Cell Death in L929 Cells by ABP 501 as Compared to Adalimumab	Murine L929 cells (ATCC CCL-1) Recombinant human TNFα (cat#300-01A lot#0302CY25) Recombinant nonhuman primate TNFα (cat#1070-RM lot#FXU0610021)	*In vitro* assays measuring inhibition of TNFα-induced cytotoxicity in L929 cells ABP 501 DP lots #0010085289 Adalimumab (EU) Adalimumab (US)	**First experiment (human TNF) replicates from a single lot of each material** ABP 501 = 390, 240, 343 pM adalimumab (US) = 1355, 284, 291 pM adalimumab (EU) = 2018, 294, 407 pM

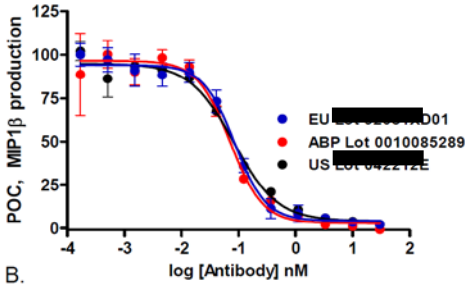
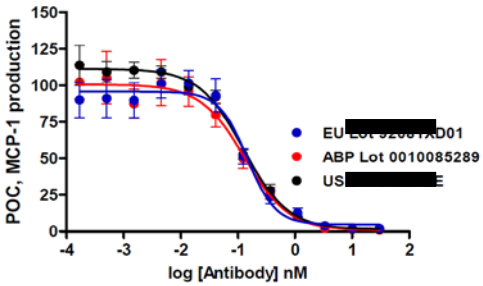
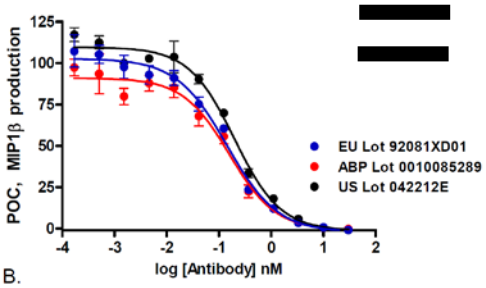
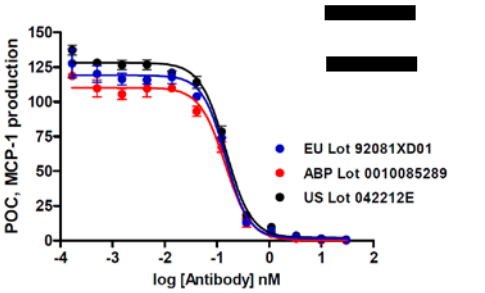
			A.  B.  (A) = inhibition of human TNFα-induced cell death (B) = inhibition of cynomolgus monkey TNFα-induced cell death adalimumab (EU) = Humira®, which is approved and marketed in the European Union; adalimumab (US) = Humira®, which is approved and marketed in the United States; TNFα = tumor necrosis factor alpha. Each point is a mean of 3 within-assay replicates ± standard error of the mean. Source: Research Report: R20120008
R20120149 Neutralization of Human TNF alpha-induced Cell Death in L929 Cells by Multiple Lots of ABP 501 and Adalimumab	Murine L929 cells (ATCC CCL-1) Recombinant human TNFα (cat no. 300-01A, lot no. 0302CY25)	Cytotoxicity assay ABP 501 DP lots 0010085289, 0010085295, and 0010085297 Adalimumab (US) Adalimumab (EU)	**ABP 501 EC_{50}**= 511, 457, 454 pM **adalimumab (US) EC_{50}**= 379, 391, 544 pM **adalimumab (EU) EC_{50}**= 356, 306, 338 pM
Inhibition of proliferation in a Mixed Lymphocyte Reaction (MLR)			
R20140036 Inhibition of Proliferation in a (MLR) by ABP 501, adalimumab (US) and adalimumab (EU)	Recombinant human TNFα Frozen peripheral blood mononuclear cells (PBMC) from healthy volunteer donors	allogeneic mixed lymphocyte reaction (MLR) ABP 501 Drug Product lots 10112898 (47.9 mg/mL), 10155776 (48.5 mg/mL) and 10155784 (51.0 mg/mL) Adalimumab (US) Adalimumab (EU)	 adalimumab (EU) = Humira®, which is approved and marketed in the European Union; adalimumab (US) = Humira®, which is approved and marketed in the United States; CPM = counts per minute; mAb = monoclonal antibody; MLR = mixed lymphocyte reaction. Each point is an individual test, with n = 5 replicates per mAb sample and n = 10 replicates in the no antibody sample. Each column of data points represents a unique lot of test mAb. Source: Research Report R20140036

FcγR Binding			
Study R20120003 FcγRIIIa (158V) Binding Analysis of ABP501, US and EU Adalimumab in the presence of human TNFα	FcγRIIIa (158V) AlphaLISA® competitive binding assay in the presence of human TNFα	Test Sample / Lot # / Conc. (mg/mL) ABP 501 (Ref Std and CT) 0010085289 51.1 ABP 501 0010085288 50.2 ABP 501 0010085295 52.6 ABP 501 0010085297 50.0 Adalimumab (US) [redacted] 52.3 Adalimumab (US) 53.1 Adalimumab (US) 51.1 Adalimumab (EU) [redacted]14 50.9 Adalimumab (EU) [redacted]02 51.6 Adalimumab (EU) 92081XD01 50.6	**Figure 10. Dose-response Curves from FcγRIIIa AlphaLISA Assay in the presence of TNFα Assay 1 (16 Nov 2011)**  Non-constrained dose-response curves from FcγRIIIa AlphaLISA with TNF α Assay 1 initiated 16 Nov 2011. Independent preparations of ABP 501 lead lot# 0010085289 were used as the assay reference standard and control. Each dose point represents the mean of three within-assay replicates ± standard deviation. **Table 8. FcγRIIIa(158V) Binding Assay with TNFα Summary of ABP 501, Adalimumab (US), and Adalimumab (EU)** % Relative Binding to FcγRIIIa Sample / Assay 1 / Assay 2 / Assay 3 / Mean (SD) / % CV ABP 501 Lot 0010085288 98.9 103.0 122.0 108 (12.3) 11.4 Adalimumab (US) [redacted] 89.3 98.1 116.0 101 (13.6) 13.5 Adalimumab (EU) [redacted] 120.0 105.0 115.0 113 (7.6) 6.7 adalimumab (EU) = Humira®, which is approved and marketed in the European Union; adalimumab (US) = Humira®, which is approved and marketed in the United States; CV = coefficient of variation; FcγRIIIa = Fc gamma receptor Type IIIa; SD = standard deviation; TNFα = tumor necrosis factor alpha. Source: Research Report R20120003
Study R20140023 FcγRIIIa (158F) Binding Analysis of ABP 501, US and EU Adalimumab	In vitro competitive binding assay	Test Sample / Lot # / Conc. (mg/mL) ABP 501 (RS and CT) 0010085289 51.1 ABP 501 0010112898 47.9 ABP 501 0010155776 48.5 ABP 501 0010155784 51.0 Adalimumab (US) [redacted] 50.2 Adalimumab (US) 48.0 Adalimumab (US) 50.3 Adalimumab (EU) 50.5 Adalimumab (EU) 24356XH10 49.9 Adalimumab (EU) 27383XH01 52.3	 % Relative Binding to FcγRIIIa (158F) Sample / Assay 1 / Assay 2 / Assay 3 / Mean / STDEV / %CV ABP Lot 0010112898 73.8 72.0 74.1 73 1.1 2 ABP Lot 001055776 91.1 90.7 96.1 93 3.0 3 ABP Lot 0010155784 86.5 79.6 93.9 87 7.2 8 US [redacted] 81.8 80.8 87.3 83 3.5 4 US [redacted] 96.8 90.1 97.4 95 4.1 4 US Lot 261512E 84.3 84.5 84.4 84 0.1 0 EU [redacted]03 91.3 107.7 95.8 98 8.5 9 EU [redacted]10 89.4 95.0 83.9 89 5.6 6 EU Lot 27383XH01 83.1 98.0 83.0 88 8.6 10

<table>
<tr>
<td>Study R20140021
FcγRIa Binding Analysis of ABP501, US and EU Adalimumab</td>
<td>In vitro competitive binding assay</td>
<td>
<table>
<tr><th>Test Sample</th><th>Lot #</th><th>Conc. (mg/mL)</th></tr>
<tr><td>ABP 501 (Ref Std and CT)</td><td>0010085289</td><td>51.1</td></tr>
<tr><td>ABP 501</td><td>0010112898</td><td>47.9</td></tr>
<tr><td>ABP 501</td><td>0010155776</td><td>48.5</td></tr>
<tr><td>ABP 501</td><td>0010155784</td><td>51.0</td></tr>
<tr><td>Adalimumab (US)</td><td>[redacted]</td><td>50.2</td></tr>
<tr><td>Adalimumab (US)</td><td>[redacted]</td><td>48.0</td></tr>
<tr><td>Adalimumab (US)</td><td>[redacted]</td><td>50.3</td></tr>
<tr><td>Adalimumab (EU)</td><td>[redacted]</td><td>50.5</td></tr>
<tr><td>Adalimumab (EU)</td><td>24356XH10</td><td>49.9</td></tr>
<tr><td>Adalimumab (EU)</td><td>27383XH01</td><td>52.3</td></tr>
</table>
</td>
<td>


<table>
<tr><th colspan="7">% Relative Binding to FcγRIa</th></tr>
<tr><th>Sample</th><th>Assay 1</th><th>Assay 2</th><th>Assay 3</th><th>Mean</th><th>SD</th><th>% CV</th></tr>
<tr><td>ABP 501 Lot 0010112898</td><td>97.6</td><td>98.2</td><td>102.0</td><td>99</td><td>2.4</td><td>2</td></tr>
<tr><td>ABP 501 Lot 0010155776</td><td>98.1</td><td>95.1</td><td>99.3</td><td>98</td><td>2.2</td><td>2</td></tr>
<tr><td>ABP 501 Lot 0010155784</td><td>100.8</td><td>90.7</td><td>97.2</td><td>96</td><td>5.1</td><td>5</td></tr>
<tr><td>Adalimumab (US) [redacted]</td><td>93.6</td><td>89.5</td><td>93.8</td><td>92</td><td>2.4</td><td>3</td></tr>
<tr><td>Adalimumab (US) [redacted]</td><td>97.3</td><td>92.0</td><td>98.0</td><td>96</td><td>3.3</td><td>3</td></tr>
<tr><td>Adalimumab (US) [redacted]</td><td>94.8</td><td>91.9</td><td>98.8</td><td>95</td><td>3.5</td><td>4</td></tr>
<tr><td>Adalimumab (EU) [redacted]</td><td>92.0</td><td>91.6</td><td>93.1</td><td>92</td><td>0.8</td><td>1</td></tr>
<tr><td>Adalimumab (EU) [redacted]</td><td>97.1</td><td>90.8</td><td>93.3</td><td>94</td><td>3.2</td><td>3</td></tr>
<tr><td>Adalimumab (EU) [redacted]</td><td>99.1</td><td>88.3</td><td>93.8</td><td>94</td><td>5.4</td><td>6</td></tr>
</table>
</td>
</tr>
<tr>
<td>Study R20140022
FcγRIIa Binding Analysis of ABP501, US and EU Adalimumab</td>
<td>In vitro competitive binding assay</td>
<td>
<table>
<tr><th>Test Sample</th><th>Lot #</th><th>Conc. (mg/mL)</th></tr>
<tr><td>ABP 501 (Ref Std and CT)</td><td>0010085289</td><td>51.1</td></tr>
<tr><td>ABP 501</td><td>0010112898</td><td>47.9</td></tr>
<tr><td>ABP 501</td><td>0010155776</td><td>48.5</td></tr>
<tr><td>ABP 501</td><td>0010155784</td><td>51.0</td></tr>
<tr><td>Adalimumab (US)</td><td>[redacted]</td><td>50.2</td></tr>
<tr><td>Adalimumab (US)</td><td>[redacted]</td><td>48.0</td></tr>
<tr><td>Adalimumab (US)</td><td>[redacted]</td><td>50.3</td></tr>
<tr><td>Adalimumab (EU)</td><td>[redacted]</td><td>50.5</td></tr>
<tr><td>Adalimumab (EU)</td><td>24356XH10</td><td>49.9</td></tr>
<tr><td>Adalimumab (EU)</td><td>27383XH01</td><td>52.3</td></tr>
</table>
</td>
<td>


adalimumab (EU) = Humira®, which is approved and marketed in the European Union; adalimumab (US) = Humira®, which is approved and marketed in the United States; FcγRIIa = Fc gamma receptor Type IIa; RLU = relative luminescence unit.
Independent preparations of ABP 501 Lot 0010085289 were used as the assay reference standard and control. Each dose point represents the mean of 3 within-assay replicates ± standard deviation.
Source: Research Report R20140022
</td>
</tr>
<tr><td colspan="4">Human and NHP TNFα Inhibition in Human Whole Blood</td></tr>
</table>

R20120009 Comparative Neutralization of TNFa-Induced MIP-1 R and MCP-1 Production in Whole Blood by ABP 501	Ex vivo chemokine production inhibition assay in whole blood in both human and NHP cellular assays. Inhibition of TNFα-induced chemokine (MCP-1 and MIP-1β) production by ABP 501, adalimumab (US), and adalimumab (EU) in 50% whole blood. The assay was run with recombinant human TNFα in human whole blood from 3 healthy donors, and with NHP TNFα in cynomolgus monkey whole blood from 3 healthy donors.	ABP 501 Drug Product material, lots #0010085289 Adalimumab (EU) Adalimumab (US)	**Figure 9. Representative Inhibition of Human TNFα Activity in Human Whole Blood by ABP 501, Adalimumab (US), and Adalimumab (EU)** A.  B.  A) = inhibition of human TNFα-induced MIP-1 (B) = inhibition of human TNFα-induced MCP-1 MCP-1 = monocyte chemotactic protein-1; MIP-1α = macrophage inflammatory protein-1 beta; POC = percent of control; TNFα = tumor necrosis factor alpha. Each point is a mean of 3 within-assay replicates ± standard error of the mean. **Figure 10. Representative Inhibition of TNFα Activity in Nonhuman Primate Whole Blood by ABP 501, Adalimumab (US), and Adalimumab (EU)** A.  B.  A) = inhibition of NHP TNFα-induced MIP-1 (B) = inhibition of NHP TNFα-induced MCP-1 MCP-1 = monocyte chemotactic protein-1;

<table>
<tr><td></td><td></td><td></td><td>MIP-1α = macrophage inflammatory protein-1 beta; POC = percent of control; TNFα = tumor necrosis factor alpha. Each point is a mean of 3 within-assay replicates ± standard error of the mean.</td></tr>
<tr><td>R20120151
Neutralization of Human TNF alpha-induced MIP-1 Beta and MCP-1 Production in
Human Whole Blood by Multiple Lots of ABP 501 and Adalimumab</td><td>Ex vivo chemokine production inhibition assay in whole blood</td><td>ABP 501
Drug Product material, lots 0010085295 and 0010085297

Adalimumab (US)

Adalimumab (EU)</td><td>
<table>
<tr><th></th><th>MIP-1β EC_{50} (pM)</th><th>MIP-1β EC_{50} (pM)</th><th>MIP-1β EC_{50} (pM)</th><th>MCP-1 EC_{50} (pM)</th><th>MCP-1 EC_{50} (pM)</th><th>MCP-1 EC_{50} (pM)</th></tr>
<tr><td></td><td>Donor 1194</td><td>Donor 1240</td><td>Donor 1452</td><td>Donor 1194</td><td>Donor 1240</td><td>Donor 1452</td></tr>
<tr><td>ABP501 lot 0010085295</td><td>74</td><td>55</td><td>43</td><td>134</td><td>48</td><td>36</td></tr>
<tr><td>Adalimumab (US) [redacted]</td><td>75</td><td>79</td><td>33</td><td>90</td><td>49</td><td>25</td></tr>
<tr><td>Adalimumab (EU) [redacted]</td><td>67</td><td>61</td><td>27</td><td>61</td><td>33</td><td>27</td></tr>
<tr><td></td><td>Donor 1073</td><td>Donor 1096</td><td>Donor 1328</td><td>Donor 1073</td><td>Donor 1096</td><td>Donor 1328</td></tr>
<tr><td>ABP501 lot 0010085297</td><td>68</td><td>50</td><td>67</td><td>54</td><td>63</td><td>62</td></tr>
<tr><td>Adalimumab (US) [redacted]</td><td>65</td><td>56</td><td>72</td><td>65</td><td>70</td><td>63</td></tr>
<tr><td>Adalimumab (EU) [redacted]</td><td>77</td><td>65</td><td>84</td><td>77</td><td>74</td><td>65</td></tr>
</table>
Data shown are mean of n = 3 assay replicates.
Source: ELN 20120622-00031 and 20120622-00035
</td></tr>
</table>

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

Safety pharmacology programme

No safety pharmacology studies have been submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

2.3.3. Pharmacokinetics

A toxicokinetic evaluation was performed as part of a repeat dose toxicity program in cynomolgus monkeys, please see toxicology section below. There was no meaningful difference in TK parameters between animals dosed with ABP 501 and adalimumab (US).

Distribution

No distribution studies were submitted in line with the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

Metabolism

No metabolism studies have been conducted with adalimumab. These are not considered relevant for a therapeutic protein because the expected consequence of metabolism is the normal catabolic

degradation to small peptides and individual amino acids. As such, classical biotransformation studies performed for small molecules are not warranted per current regulatory guidance (ICH S6).

Excretion

No excretion studies have been conducted with ABP 501; no specific studies were undertaken to evaluate the excretion of ABP 501 in breast milk either. However, all immunoglobulin G subclasses can be transferred into the milk of lactating animals, has been reported into the literature; in light of this evidence, it can be deducted that ABP 501 is excreted in lactation fluid.

Drug-drug Interactions

No non-clinical or clinical dedicated drug-drug interactions studies were conducted, in order to assess the effect of concomitant drugs on ABP 501 PK which was considered acceptable by the CHMP.

2.3.4. Toxicology

Single dose toxicity

According to the CHMP/EMA guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010), the conduct of repeated dose toxicity studies in non-human primates is not recommended for biosimilar products (this is also in line with Scientific Advice provided).

Repeat dose toxicity

Two one month comparative repeat dose toxicity studies with weekly SC dosing were performed in cynomolgus monkeys with ABP 501 and adalimumab (US).

The first was interrupted after two doses and only limited toxicity information was acquired in this study. In the second study, monkeys were dosed SC with 157 mg/kg ABP 501, adalimumab or vehicle. The dose was similar to the highest dose in the Humira development program.

Table 2- Repeat-dose toxicity studies

Study ID / GLP	Species / Sex / Number / Group	Dose / Route	Duration	NOEL / NOAEL (mg / kg / day)	Major findings
Amgen Study No. 114832 / GLP	Cynomolgus Monkey (5 M /group) 2.7 to 3.6 years	32 mg/kg s.c. ABP 501 (0010085288), and adalimumab US	Study terminated prematurely after 2 doses*	NA	There were no clinical signs or changes in body weights, or clinical pathology parameters (serum chemistry, hematology, and coagulation).

Study ID / GLP	Species / Sex / Number / Group	Dose / Route	Duration	NOEL / NOAEL (mg / kg / day)	Major findings
Amgen Study No. 115674 / GLP	Cynomolgus Monkey (3/sex/group) 3.0 to 3.7 years males (2.5 to 3.5 kg) and 3.0 to 4.0 years females (2.6 to 3.0 kg)	0 mg/kg (Vehicle) 157 mg/kg ABP 501 (0010085288), and 157 mg/kg Adalimumab (US)	One month (4 s.c. weakly administr)	NA	↑ (limited to transient minimal to mild) neutrophil counts and (minimal to moderate) fibrinogen concentration (ABP 501 and adalumumab US day 4) ↑ incidences of decreased size and number of germinal centers in axillary lymph node, mesenteric lymph node, and tonsil (ABP 501 and adalumumab US).

Genotoxicity

No genotoxicity studies were submitted in line with the CHMP guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005).

Carcinogenicity

Carcinogenicity studies were not submitted in line with the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010), and the CHMP guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005).

Reproduction Toxicity

Reproductive and developmental toxicity studies were not submitted, in line with the CHMP Guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/ 403543/2010), and the CHMP guidance on biosimilar medicinal products (EMEA/CHMP/BMWP/42832/2005).

Local Tolerance

Histologic examination of the SC injection site was performed as part of the 1-month toxicology study in monkeys. Effects at the SC injection site (focal fibroplasia/fibrosis and focal mononuclear or mixed cell infiltrates) were considered secondary to the injection procedure since they are commonly observed at injection sites and were noted at a similarly low incidence in vehicle control, ABP 501, and adalimumab (US) groups. Although ABP 501 and adalimumab (US) have different formulations, there was no apparent difference in local tolerance between the two drug products.

2.3.5. Ecotoxicity / environmental risk assessment

The Applicant provided a justification for not submitting any environmental risk assessment studies based on the fact that AMGEVITA is a protein and therefore unlikely to pose a significant risk to the environment which is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.3.6. Discussion on non-clinical aspects

For the *in vitro* biological biosimilarity evaluation a limited number of methods for more extensive comparisons were submitted. These studies are assessed in the Quality section of the report. These methods are considered to contain all the important elements for the biosimilarity evaluation and are considered pivotal for this purpose.

Additional studies were performed with less stringently characterized methods and with no more than 3 lots from each product.

No differences in activity between ABP 501 and adalimumab (EU) or adalimumab (US) could be detected in any of these assays.

It is clear that a number of these assays are of limited quantitative strength and would only detect large differences. The cellular assays and whole blood assays presented in this section are in most cases of such nature. The MLR assay is stated to give only qualitative information. For other cellular assays, although variable origin of cells or blood resulted in assay variability, a consistent and similar activity of the different adalimumab lots was shown.

In addition to the functionally most important Fc receptor types (FcRn and FCRIIIa), other members of the Fc receptor class were studied in this section. These assays were performed with similar methodology as the pivotal assays. Although a limited number of lots were tested in these assays, similarity was consistently shown.

An assay program covering a broad spectrum of both TNFα and IgG related biological activities did not reveal any differences that could be of biological importance.

A toxicokinetic evaluation was performed as part of a repeat dose toxicity program in cynomolgus monkeys. There was no meaningful difference in TK parameters between animals dosed with ABP 501 and adalimumab (US). This study showed similar pharmacodynamic lymphoid changes for ABP 501 and adalimumab (US), characterized by mild to moderate decreased size and number of germinal centers in lymph nodes. No unexpected toxicities were observed with ABP 501. While supportive for the biosimilarity evaluation, more weight is put on the human PK data.

In the EU guideline on biosimilar monoclonal antibodies, it is pointed out that non-human primate toxicity studies are considered of limited value for biosimilarity evaluation and such studies are not generally recommended. The small format of these studies lacks any power to detect differences of potential clinical importance. It is however acknowledged that these studies were performed to fulfil the requirements in other regions.

2.3.7. Conclusion on the non-clinical aspects

Comparative pharmacodynamics, pharmacokinetic and toxicology data demonstrated biosimilarity between AMGEVITA and the reference product Humira. The provided non-clinical comparability exercise testing strategy was considered as appropriate. Relevant regulatory guidelines were taken into consideration.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report/ Location
Healthy Subject PK and Initial Tolerability Study Reports (Module 5.3.3.1)								
PK similarity	20110217	PK similarity, safety, tolerability, immunogenicity and bridging between adalimumab (US) and adalimumab (EU)	Phase 1 randomized, single-blind, single-dose, 3-arm, parallel group	ABP 501 vs adalimumab (US) vs adalimumab (EU) 40 mg SC, once	203 (67 ABP 501, 69 adalimumab [US], 67 adalimumab [EU])	Healthy subjects	Single dose	Complete; CSR/ Module 5.3.3.1 20110217

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report/ Location
Efficacy and Safety	20120263	Efficacy, safety, immunogenicity, PK	Phase 3, randomized, double-blind, active comparator-controlled Subjects qualifying for re-randomization at wk 16: ABP 501 group continued treatment with ABP 501; Adalimumab group re-randomized to adalimumab or ABP 501	ABP 501 vs adalimumab (EU), 80 mg SC, wk 1/ day 1, then 40 mg SC every other wk beginning at wk 2	350 175 ABP 501, 175 adalimumab	Men and women ≥ 18 to ≤ 75 yrs of age Moderate to severe Ps for ≥ 6 mos BSA ≥ 10% involved PASI ≥ 12 sPGA ≥ 3 Subjects achieving ≥ PASI 50 response at wk 16 qualified for re-randomization	52 wks	Complete; CSR/ Module 5.3.5.1 20120263

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report/ Location
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1)								
Efficacy and Safety	20120262	Efficacy, safety, immunogenicity, PK	Phase 3 randomized, double-blind, active comparator-controlled	ABP 501 vs adalimumab (US), 40 mg SC, every other wk	526 264 ABP 501, 262 adalimumab	Men and women ≥ 18 to ≤ 80 yrs of age Moderate to severe RA for ≥ 3 mos ≥ 6 swollen joints and ≥ 6 tender joints ESR ≥ 28 mm/hr or CRP > 1.0 mg/dL Received MTX ≥ 12 wks and on stable dose ≥ 8 wks	26 wks	Complete; CSR/ Module 5.3.5.1 20120262

2.4.2. Pharmacokinetics

Three trials have been submitted in order to demonstrate pharmacokinetic biosimilarity:

- Study 20110217 which was a single-dose phase 1, 3-way pharmacokinetic (PK) similarity study in healthy men and women comparing ABP 501 with adalimumab (EU) and adalimumab (US)
- 2 randomized, double-blind, active comparator-controlled phase 3 studies including comparison of trough serum concentrations (sparse sampling):
    - Study 20120262 in adult subjects with moderate to severe RA comparing ABP 501 with adalimumab (US)
    - Study 20120263 in subjects with moderate to severe psoriasis comparing ABP 501 with adalimumab (EU)

Pharmacokinetic Study 20110217

The study was a randomised, 3-arm, single-blind, single-dose parallel group study in healthy adult male and female subjects. Each subject received a single 40-mg (0.8 ml) subcutaneous dose of ABP 501, adalimumab (US), or adalimumab (EU) 50 mg/ml solution for injection in a pre-filler syringe (40 mg/0.8 ml) in the morning of day 1 following a light break-fast. Blood-samples for analysis of active substance were taken pre-dose and 1, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 240, 312, 360, 504, 672, 840, 1008, 1176, 1344 and 1488 hours after drug administration. Blood samples for analysis of antibodies capable of binding adalimumab were taken pre-dose and day 16, 29 and 63. A total of 203 adult healthy male (116) and female (87) volunteers aged 18-45 years were enrolled. There were 7 subjects who prematurely discontinued the study and thus 196 subjects (96.6%) completed the study.

The mean serum concentration-time profiles were similar following a single SC injection of all 3 treatments over the entire course of sampling.

The results are presented below.

Figure 1- Mean (+SD) serum ABP 501, adalimumab (US) and adalimumab (EU) concentration time profiles

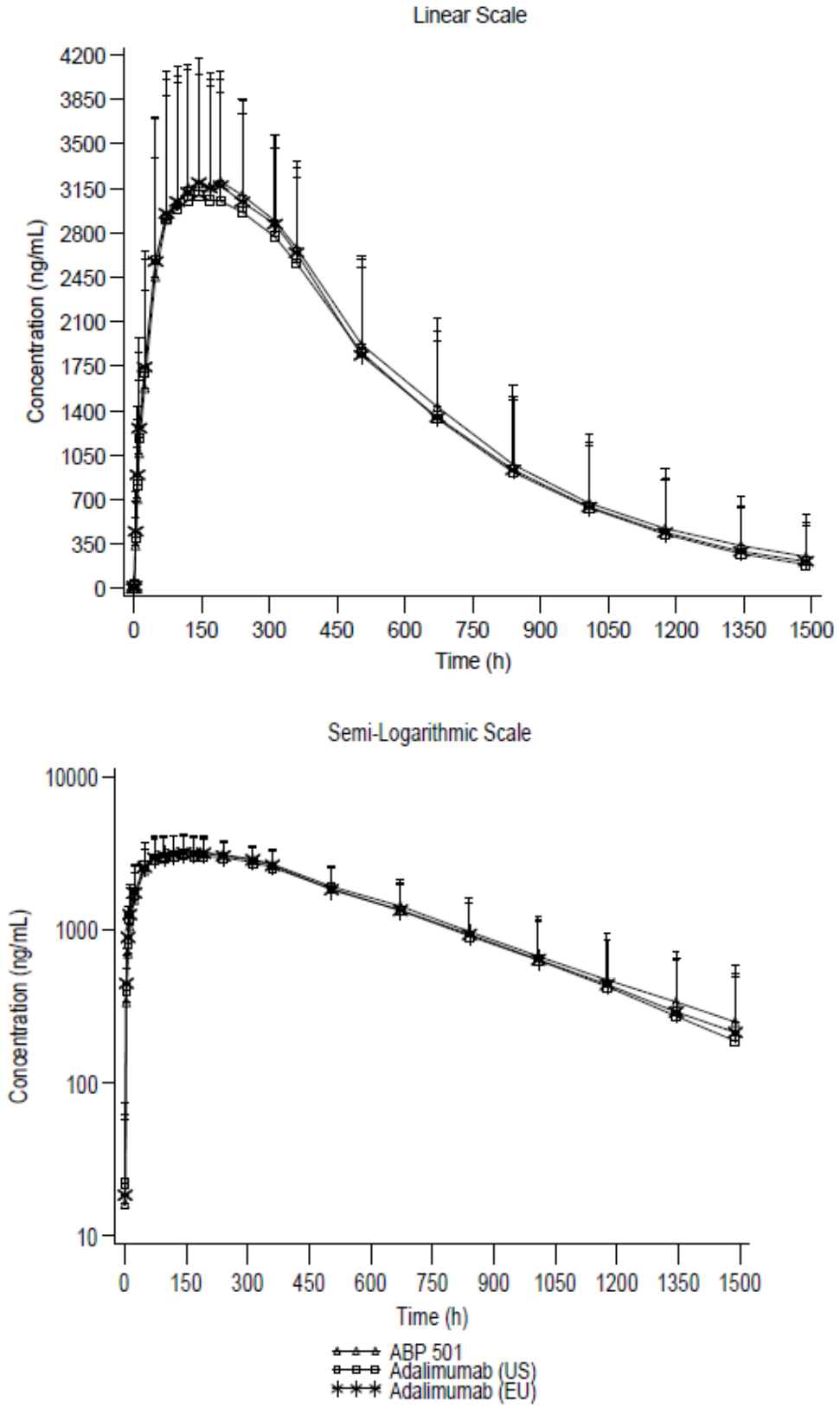


Table 3- Pharmacokinetic parameters for ABP 501, adalimubab (US) and adalimumab (EU) in study 20110217

Treatment	C_{max} (µg/ml) GM [n] (GeoCV%)	AUC_{last} (µg.h/mL) GM [n] (GeoCV%)	AUC_{inf} (µg.h/mL) GM [n] (GeoCV%)	t_{max} (h) Median [n] (Min-Max)	$t_{½}$ (h) Mean [n] (SD)
ABP 501	3.27 [67] (30.2)	2020 [67] (38.6)	2150 [58] (36.9)	191 [67] (47.2 - 360)	246 [58] (160)
Adalimumab (US)	3.14 [69] (32.7)	1890 [69] (41.8)	1920 [61] (39.8)	144 [69] (47.0 - 359)	215 [61] (121)
Adalimumab (EU)	3.28 [67] (30.5)	1980 [66] (38.3)	2010 [57] (41.7)	168 [67] (48.0 - 313)	233 [57] (151)

Abbreviations: GeoCV% = geometric mean coefficient of variation; GM = geometric mean; Max = maximum; Min = minimum; n = number of nonmissing observations; SD = standard deviation

Table 4- Statistical assessment of ABP 501, adalimumab (US) and adalimumab (EU)

Treatment and Comparison	C_{max} (µg/mL) Adjusted LS Geometric Mean [n]	AUC_{inf} (µg.h/mL) Adjusted LS Geometric Mean [n]	AUC_{last} (µg.h/mL) Adjusted LS Geometric Mean [n]
ABP 501	3.22 [67]	2140 [58]	2000 [67]
Adalimumab (US)	3.11 [69]	1920 [61]	1880 [69]
Adalimumab (EU)	3.37 [67]	2050 [57]	2020 [66]
	Ratio of Adjusted LS Geometric Means (90% CI)		
ABP 501 vs. Adalimumab (US)	1.04 (0.964, 1.12)	1.11 (1.00, 1.24)	1.07 (0.964, 1.18)
ABP 501 vs. Adalimumab (EU)	0.96 (0.889, 1.03)	1.04 (0.935, 1.17)	0.99 (0.892, 1.10)
Adalimumab (US) vs. Adalimumab (EU)	0.92 (0.857, 0.994)	0.94 (0.840, 1.04)	0.93 (0.836, 1.03)

Abbreviations: CI = confidence interval; LS = least squares; n = number of nonmissing observations

The extrapolated AUC was less than 20% in most subjects. No pre-dose concentrations were detected and no subjects reached t_{max} at the first sampling point.

Overall exposure was approximately 20% to 30% lower for all 3 treatments in ADA-positive subjects compared to ADA-negative subjects, and consistent with the lower exposure was the shorter t½ in ADA-positive subjects. On average, the t½ was 6 to 7 days in the ADA-positive subjects compared to 12 to 15 days in those subjects who were ADA negative. When comparing ABP 501 to adalimumab (EU) in subjects classified as ADA negative, the 90% CIs of the ratios of geometric means were fully contained within 0.80 to 1.25.

Table 5 - Summary of pharmacokinetic parameters by antibody status

Treatment	C_{max} (µg/ml) GM [n] (GeoCV%)	AUC_{last} (µg.h/mL) GM [n] (GeoCV%)	AUC_{inf} (µg.h/mL) GM [n] (GeoCV%)	t_{max} (h) Median [n] (Min-Max)	$t_{½}$ (h) Mean [n] (SD)
			ADA Positive		
ABP 501	3.24 [36] (31.5)	1730 [36] (36.6)	1840 [33] (27.2)	168 [36] (71.0 - 312)	151 [33] (75.1)
Adalimumab (US)	3.21 [38] (33.0)	1730 [38] (39.8)	1790 [36] (41.8)	143 [38] (47.0 - 311)	169 [36] (99.1)
Adalimumab (EU)	3.33 [45] (31.8)	1820 [44] (40.1)	1820 [40] (40.9)	168 [45] (48.0 - 313)	176 [40] (96.8)
			ADA Negative		
ABP 501	3.31 [31] (29.1)	2430 [31] (31.4)	2650 [25] (37.3)	191 [31] (47.2 - 360]	371 [25] (156)
Adalimumab (US)	3.06 [31] (32.8)	2110 [31] (41.9)	2130 [25] (34.8)	167 [31] (71.1 - 359)	281 [25] (122)
Adalimumab (EU)	3.17 [22] (28.1)	2360 [22] (26.9)	2540 [17] (32.8)	144 [22] (72.0 - 312)	366 [17] (175)

Abbreviations: ADA = antidrug antibody; GeoCV% = geometric mean coefficient of variation; GM = geometric mean; Max = maximum; Min = minimum; n = number of nonmissing observations; SD = standard deviation

Table 6- Summary of Statistical Assessment of ABP 501, adalimumab (US) and adalimumab (EU) pharmacokinetic parameters in antidrug antibody negative subjects

Treatment and Comparison	C_{max} (µg/mL) Adjusted LS Geometric Mean [n]	AUC_{inf} (µg.h/mL) Adjusted LS Geometric Mean [n]	AUC_{last} (µg.h/mL) Adjusted LS Geometric Mean [n]
ABP 501	3.22 [31]	2590 [25]	2370 [31]
Adalimumab (US)	3.07 [31]	2180 [25]	2120 [31]
Adalimumab (EU)	3.29 [22]	2560 [17]	2440 [22]
		Ratio of Adjusted LS Geometric Means (90% CI)	
ABP 501 vs. Adalimumab (US)	1.05 (0.947, 1.16)	1.19 (1.03, 1.37)	1.12 (0.988, 1.27)
ABP 501 vs. Adalimumab (EU)	0.98 (0.875, 1.09)	1.01 (0.865, 1.18)	0.97 (0.844, 1.11)
Adalimumab (US) vs. Adalimumab (EU)	0.93 (0.836, 1.04)	0.85 (0.727, 0.992)	0.87 (0.755, 0.992)

Abbreviations: CI = confidence interval; LS = least squares; n = number of nonmissing observations

A sensitivity analysis was performed with correction of PK parameters for protein content in each test/reference product. In this case the 90% confidence intervals for the ratios were within 0.80-1.25 for AUC_{0-t} and C_{max} while for $AUC_{0-\infty}$ the upper limit was above 1.25.

Table 7 - Summary of statistical assessment of ABP 501, Adalimumab (US) and Adalimumab (EU) pharmacokinetic parameters adjusted by protein content factor

Treatment and Comparison	C_{max} (µg/mL) Adjusted LS Geometric Mean [n]	AUC_{inf} (µg.h/mL) Adjusted LS Geometric Mean [n]	AUC_{last} (µg.h/mL) Adjusted LS Geometric Mean [n]
ABP 501	3.37 [67]	2230 [58]	2090 [67]
Adalimumab (US)	3.12 [69]	1920 [61]	1880 [69]
Adalimumab (EU)	3.16 [67]	1920 [57]	1900 [66]
	Ratio of Adjusted LS Geometric Means (90% CI)		
ABP 501 vs Adalimumab (US)	1.08 (1.00, 1.16)	1.16 (1.04, 1.29)	1.11 (1.00, 1.23)
ABP 501 vs. Adalimumab (EU)	1.07 (0.989, 1.15)	1.16 (1.04, 1.30)	1.10 (0.993, 1.22)
Adalimumab (US) vs. Adalimumab (EU)	0.99 (0.918, 1.06)	1.00 (0.899, 1.12)	0.99 (0.895, 1.10)

Abbreviations: CI = confidence interval; LS = least squares; n = number of nonmissing observations

All samples were tested for binding antibodies against the three different sources of adalimumab (ABP 501, adalimumab (US) and adalimumab (EU)). The three assays performed similarly for all samples, indicating that the anti-adalimumab antibodies are not specific for one source of adalimumab.

The binding antibody incidence by treatment was similar for ABP 501 (54%) and adalimumab (US) (55%). The incidence for subjects treated with a single dose of adalimumab (EU) was higher (67%). Neutralizing activity was tested only against ABP 501, as the binding antibody assay demonstrated the detected ADAs had equivalent binding capability to ABP 501 and adalimumab (US and EU). The neutralizing antibody incidence by treatment during the study was similar for ABP 501 (18%), adalimumab (US) (22%), and adalimumab (EU) (21%).

Table 8- Antidrug antibody incidence by treatment and by assay (study 20110217 safety analysis population)

	Binding Antibody Assay Positive (In-study Only)[a]				Neutralizing Activity Positive[a]
Treatment	ABP 501 % (n/N)	Adalimumab (US) % (n/N)	Adalimumab (EU) % (n/N)	Any assay % (n/N)	In-study only % (n/N)
ABP 501	46 (31/67)	45 (30/67)	51 (34/67)	54 (36/67)	18 (12/67)
Adalimumab (US)	49 (34/69)	48 (33/69)	52 (36/69)	55 (38/69)	22 (15/69)
Adalimumab (EU)	67 (45/67)	63 (42/67)	61 (41/67)	67 (45/67)	21 (14/67)
Any treatment	54 (110/203)	52 (105/203)	55 (111/203)	59 (119/203)	20 (41/203)

CSR = clinical study report; EU = European Union; US = United States.
[a] Follow-up binding antibody and all neutralizing activity samples were tested against ABP 501 only; 4 additional subjects tested positive for ABP 501 binding antibodies during follow-up.

Phase 3 study 20120263 (psoriasis)

The study is described in the Clinical Efficacy section below. The pharmacokinetic results are summarised in this section.

From baseline to week 16, the geometric mean trough serum concentrations were considered to be similar between Treatment Group A (ABP 501) and Treatment Group B (adalimumab) since no notable difference in mean geometric ratios were observed. From baseline to the end of study, the geometric mean trough serum concentrations were considered to be similar between all re-randomized treatment groups across the various assessed time-points since no notable difference in geometric mean ratios was observed between any of the treatment groups.

Table 9- Geometric mean summary of trough serum concentrations (ng/ml) by visit and treatment – baseline to week 16

Timepoint	Treatment Group A (ABP 501) (N = 174)	Treatment Group B (Adalimumab) (N = 173)
Week 4		
n	166	168
Geometric Mean	4728.38	4956.31
Geometric CV (%)	69.89	70.11
GMR	0.95	
90% CI	(0.86, 1.06)	
Week 16		
n	139	131
Geometric Mean	4204.38	4057.78
Geometric CV (%)	229.50	219.62
GMR	1.04	
90% CI	(0.81, 1.32)	

CI = confidence interval; GMR = geometric mean ratio
Note: Geometric mean, geometric mean ratio and 90% CI are estimated based upon ANOVA model adjusted with stratified factors.

Table 10- Geometric mean summary of trough serum concentrations (ng/ml) by visit and treatment group – baseline to end of study

	Re-randomized		
Timepoint	Treatment Group A (ABP 501/ ABP 501) (N = 152)	Treatment Group B1 (Adalimumab/ Adalimumab) (N = 79)	Treatment Group B (Adalimumab/ ABP 501) (N = 77)
Week 4			
n	148	75	76
Geometric Mean	5017.19	4944.58	5486.99
Geometric CV (%)	66.63	62.29	63.61
GMR	1.01		1.11
90% CI	(0.90, 1.15)		(0.96, 1.28)
Week 16			
n	135	67	61
Geometric Mean	4454.44	4526.98	3786.23
Geometric CV (%)	208.71	180.74	183.04
GMR	0.98		0.84
90% CI	(0.74, 1.31)		(0.60, 1.17)
Week 20			
n	133	65	56
Geometric Mean	4410.44	4974.15	5421.73
Geometric CV (%)	165.65	144.87	146.21
GMR	0.89		1.09
90% CI	(0.69, 1.14)		(0.80, 1.48)
Week 32			
n	127	60	51
Geometric Mean	4139.61	4376.87	5156.40
Geometric CV (%)	206.00	171.95	172.34
GMR	0.95		1.18
90% CI	(0.71, 1.26)		(0.83, 1.68)
Week 52			
n	107	51	44
Geometric Mean	3097.86	3783.07	3428.72
Geometric CV (%)	198.65	167.59	166.94
GMR	0.82		0.91
90% CI	(0.60, 1.11)		(0.62, 1.31)

CI = confidence interval; GMR = geometric mean ratio
Note: Geometric mean, geometric mean ratio and 90% CI are estimated based upon ANOVA model adjusted with stratified factors.
Geometric mean ratio and 90% CI are between Treatment Group A (ABP 501/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) and between Treatment Group B2 (adalimumab/ABP 501) and Treatment Group B1 (adalimumab/adalimumab).
- Not applicable.

Phase 3 study 20120262 (RA)

The study is described in the Clinical Efficacy section further below. The pharmacokinetic results are summarised in this section. Pharmacokinetic results revealed that trough serum concentrations, the geometric mean, and the geometric coefficient of variability were similar between the ABP 501 and adalimumab groups across all study weeks, indicating that investigational product exposure was similar between treatment groups in this subject population.

Table 11- Geometric Mean Summary of Trough Serum concentrations (ng/ml) by visit and treatment

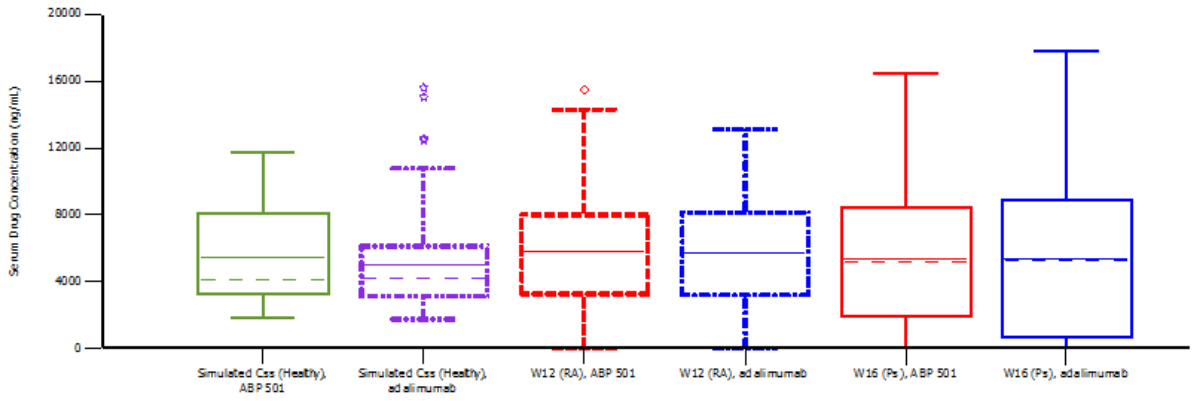
Time Point	ABP 501 (N = 264)	Adalimumab (N = 262)
Week 2		
n	247	251
Geometric Mean	2062.64	1936.11
Geometric CV (%)	61.79	61.63
Geometric mean ratio	1.07	
90% CI	(1.00, 1.14)	
Week 4		
n	247	252
Geometric Mean	3041.32	2986.43
Geometric CV (%)	106.21	105.61
Geometric mean ratio	1.02	
90% CI	(0.92, 1.13)	
Week 12		
n	231	239
Geometric Mean	4285.82	4084.96
Geometric CV (%)	211.24	210.65
Geometric mean ratio	1.05	
90% CI	(0.90, 1.22)	
Week 24		
n	224	221
Geometric Mean	4844.16	5210.75
Geometric CV (%)	189.92	189.22
Geometric mean ratio	0.93	
90% CI	(0.80, 1.08)	
Week 26		
n	210	212
Geometric Mean	3684.83	3989.68
Geometric CV (%)	182.29	183.99
Geometric mean ratio	0.92	
90% CI	(0.80, 1.07)	

CI = confidence interval
Note: Geometric mean, geometric mean ratio, and 90% CI are estimated based upon analysis of variance model adjusted with stratified factors.

Comparison between PK data in healthy volunteers and in patients

Due to differences in dosing (single dose versus multiple doses) between the PK similarity study (Study 20110217) and the 2 phase 3 studies (Study 20120262 and Study 20120263), direct comparison between single-dose PK from healthy subjects with multiple-dose trough concentrations from phase 3 studies are not relevant. Instead, the simulated trough serum concentrations of ABP 501 or adalimumab in healthy subjects at steady state following 40-mg SC Q2W dosing were estimated for comparison with the corresponding trough serum concentrations observed in the phase 3 studies (Study 20120262 in subjects with RA and Study 20120263 in subjects with Ps). Simulated values were calculated using the principle of superposition. The trough concentrations derived from the ABP 501 study in healthy subjects are highly consistent with those observed from the ABP 501 studies in RA and Ps subjects as well as between ABP 501 and adalimumab, indicating consistency in PK of ABP 501 (and comparability with adalimumab) across the 3 populations studied.

Table 12 - Serum trough concentration comparisons (study 20110217, 20120262 abd 20120263 PK analysis sets)



Note: Trough concentrations for subjects in Study 20110217 are projected. Trough at steady state was calculated based on serum concentrations observed at 312 hours and half-live values calculated by NCA. The overall formula is as follows: $1/(1-\exp(-0.693*14/\text{half-life in days}))*C_{312h}$. For the purpose of this analysis, the adalimumab (US) and adalimumab (EU) arms were combined. For Study 20120262 (RA population) and Study 20120263 (Ps population) observed trough data are from all subjects regardless of antibody status. Within each box, solid lines represent the median and dashed lines represent the mean.

C_{ss} = trough drug concentration at steady-state; EU = European Union; NCA = noncompartmental PK analysis; PK = pharmacokinetic; Ps = plaque psoriasis; RA = rheumatoid arthritis; US = United States; W12 = week 12; W16 = week 16.

Special populations

No studies were performed in patients with hepatic impairment and in patients with renal impairment as these are not required for a similar biological medicinal product.

Pharmacokinetic interaction studies

No PK interaction studies were performed as these are not required for a similar biological medicinal product.

2.4.3. Pharmacodynamics

Specific pharmacodynamic (PD) markers considered relevant to predicting efficacy of adalimumab in patients do not exist, although clinical endpoints that reflect the efficacy of treatment for all conditions of use for which adalimumab is indicated are well defined and accepted. Therefore, no PD markers were incorporated into the ABP 501 PK study, and clinical endpoints were utilized in the phase 3 studies in subjects with moderate to severe RA (Study 20120262) and Psoriasis (Study 20120263).

In accordance with EU guidance (EMEA/CHMP/BMWP/ 42832/2005; EMA/CHMP/BMWP/403543/2010), clinical evidence for comparability/similarity can be demonstrated by PD surrogate endpoints or clinical evidence. In case of AMGEVITA, clinical evidence for similarity was aimed to be demonstrated by clinical rather than PD endpoints.

2.4.4. Discussion on clinical pharmacology

The study design of the pharmacokinetic study (study 20110217) is satisfactory and was accepted in the CHMP advice. A parallel design is acceptable considering the long half-life of adalimumab (approximately 2 weeks) and the potential influence of immunogenicity. The use of healthy volunteers is agreed in line with the *Guideline on similar biological medicinal products containing monoclonal*

antibodies – non-clinical and clinical issues. The treatment groups were similar in age, ethnicity and BMI. Supportive PK data from the phase 3 studies in patients are also available in line with guideline recommendations. The 40 mg SC dose is the normally recommended dose (although higher initial doses are given for some indications) and the use of this dose is endorsed. Blood samples for analysis of antidrug antibodies were taken when there are still remaining drug concentrations in the blood, but the ADA assay methods used were assessed for tolerance in presence of drug.

Analysis with correction for protein content was the primary comparison according to the initial statistical analysis plan, but this was revised in a late amendment and instead the unadjusted PK parameters were used for the primary analysis.

For therapeutic proteins there is no firm guidance on content correction. This topic is addressed by EMA guideline (EMEA/CHMP/BMWP/42832/2005 Rev1) reporting: "Correction for protein content may be acceptable on a case-by-case basis if pre-specified and adequately justified, with the results from the assay of the test and reference products being included in the protocol". The difference in protein content was large when comparing the batch used as test product (95.8%) and the batch used as EU-sourced reference product (106.6%). Thus, it is considered relevant to compare protein-adjusted data.

For unadjusted AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the pre-specified acceptance range of 80.00-125.00% when comparing ABP 501 to the reference product from EU as well as from US and the 90% confidence intervals included 1. Both comparisons are important since the RA study was performed using US reference product. Also when comparing the US versus the EU reference products the results fell within the pre-specified acceptance range of 80.00-125.00% for all three parameters, although the confidence interval for C_{max} did not include 1.

For the protein content adjusted C_{max} and AUC_{last} the 90% CI fall within 0.80-1.25 and include 1. T_{max} and $t_{½}$ was similar for all three formulations. However, for AUC_{inf} the 90% CI falls outside the 0.80 – 1.25 limits and is statistically higher than both US and EU adalimumab (point estimate 16%).

A higher exposure of ABP 501 compared to the reference product was observed based on the primary parameter AUC_{inf} adjusted for protein content (point estimate 16%), which may indicate a difference in clearance and/or relative bioavailability. Since the difference in protein content was large (95.8% for test product compared to 106.6% for EU reference product) it is considered relevant to compare protein-adjusted data. Therefore the Applicant provided an extensive discussion to support the claim of PK similarity between ABP 501 and adalimumab. The reason why the protein content adjusted 90% CI of AUC_{inf} fell outside the BE margin is likely due to shortcomings in the study design, specifically the duration of PK plasma sampling was somewhat short. This resulted in exclusion of a relatively large proportion (13.3%) of the non-compartmental analysis (NCA) derived AUC_{inf} values, mostly due to a large extrapolated area (>20%). The exclusion led to increased imprecision in the comparison between the products with respect to AUC_{inf}. As a consequence biosimilarity was not concluded. To further investigate these results the Applicant employed a modelling approach using population PK analysis and it could be concluded that the current model provides an acceptable description of data and can be used for generating AUCinf values for all subjects. Statistical testing was not explicitly made in the model; rather, by modelling it was possible to generate individual predicted AUC_{inf} values for all subjects including the previously excluded subjects. The 90% CI of the geometric mean ratio of these AUC_{inf} values (ABP 501 vs adalimumab EU) was 0.98 to 1.23 (point estimate 1.10) which is similar to the CI for AUC_{last} using NCA evaluation (0.99-1.22, point estimate 1.10), i.e. indicating that if all subjects are included, the protein adjusted AUCinf is comparable between the products. The Applicant has provided additional supportive evidence from a population PK model that protein adjusted AUC_{inf} is comparable between ABP 501 and reference adalimumab. The updated pop PK model supports the

explanation that the observed difference in AUC_{inf} is caused by exclusion of data. Based on the totality of PK data, PK similarity can be concluded.

The sensitivity analysis with antidrug antibody negative subjects was within the pre-specified acceptance range for the comparison between ABP 501 and the EU reference product. It is clear that half-life and exposure is lower in subjects positive for antidrug antibodies compared to subjects negative for antidrug antibodies.

The results indicate a higher formation of binding anti-drug antibodies for adalimumab (EU) and similar formation of binding anti-drug antibodies for ABP 501 and adalimumab (US). According to the *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)* a lower immunogenicity for the biosimilar would not preclude biosimilarity.

For study 20120263 it is agreed that trough serum concentrations were similar between ABP 501 and adalimumab (EU) treatment groups since no notable difference in mean geometric ratios was observed and since the confidence intervals included 1. This supports similar exposure in this population.

For study 20120262 it is agreed that trough serum concentrations were similar between ABP 501 and adalimumab (US) treatment groups. This supports similar exposure in this population.

No new pharmacodynamic data has been submitted as part of this application. This is considered acceptable for a biosimilar application.

2.4.5. Conclusions on clinical pharmacology

The Applicant has sufficiently explained and justified the difference in exposure (protein content adjusted AUC_{inf}. Pharmacokinetic similarity has been sufficiently demonstrated between ABP 501 and the reference product). Thus biosimilarity can be concluded from a clinical pharmacology perspective

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose response studies were submitted. The selection of dose and dosing regimen for testing in Study 20120263 and Study 20120262 was based on that used in the approved indication of Ps and RA for Humira (80 mg SC initial loading dose followed by 40 mg SC every other week starting 1 week after the initial dose for Ps and 40 mg SC every other week for RA). The dosing regimen proposed for ABP 501 in adults with Ps as well as RA would be the same as that approved for Humira.

2.5.2. Main studies

A Randomized, Double-blind, Phase 3 Study of ABP 501 Efficacy and Safety Compared to Adalimumab in Subjects With Moderate to Severe Rheumatoid Arthritis (Study 20120262)

Methods

Study Participants

This study was conducted at 92 centers in 12 countries (USA, UK, Spain, Russia, Romania, Poland, Mexico, Hungary, Germany, Czech Republic, Canada, Bulgaria).

Key inclusion criteria:

- adults with a diagnosis of RA by 2010 ACR/EULAR classification criteria;
- moderate to severe RA duration of at least 3 months;
- active RA defined as 6 or more swollen joints and 6 or more tender joints (based on 66/68 joint count excluding distal interphalangeal joints) at screening and baseline and at least one of the following: erythrocyte sedimentation rate (ESR) $\geq$ 28 mm/hour; serum C-reactive protein (CRP) concentration > 1.0 mg/dL
- a positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) result at screening;
- been taking MTX for at least 12 consecutive weeks, and on a stable dose of 7.5 to 25 mg a week for at least 8 weeks, and willing to remain on a stable dose throughout the study;
- no known history of active tuberculosis; negative results for tuberculosis at screening.

Key exclusion criteria:

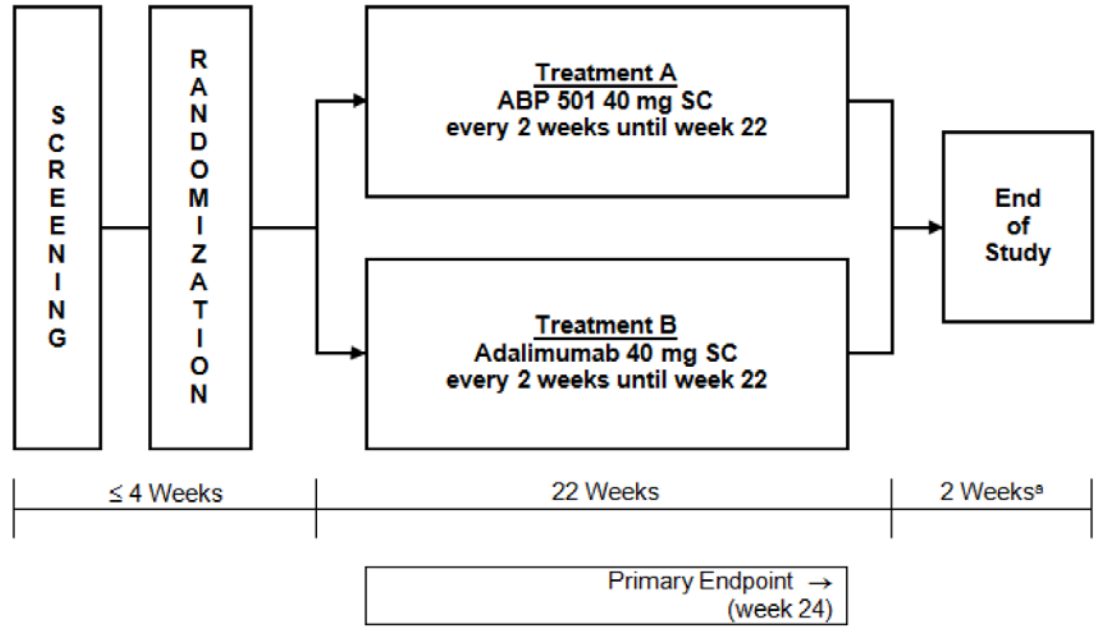
- class IV RA by ACR revised response criteria (Hochberg et al, 1992),
- Felty's syndrome;
- history of prosthetic or native joint infection;
- use of prohibited medications within 28 days prior to the first dose of IP;
- prior use of 2 or more biologic therapies for RA;
- use of specified commercially available or investigational biologic therapies for RA within the protocol-specified time frame;
- prior use of Humira or a biosimilar of Humira;
- been involved in any other investigational drug or device study within 30 days or 5 half-lives of the first dose of IP.

Women could not be pregnant or breastfeeding or plan to become pregnant while in the study or for 5 months after the last dose of IP.

The study has been conducted in a number of countries sufficiently representative of the EU population. Subjects were eligible to be enrolled in the study if they have a moderate to severe active RA, treated with MTX for at least 12 consecutive weeks. The reported inclusion criteria reflect the

target population. However, subjects were allowed to have been treated with a single previous biological agent (different to Humira or biosimilar of Humira).

Treatments



SC = subcutaneous
[a] Additional safety follow-up

Objectives

The primary objective for this study was to assess the efficacy of ABP 501 compared with adalimumab.

The secondary objectives were to assess the safety and immunogenicity of ABP 501 compared with adalimumab.

The exploratory objectives were to assess injection site pain perception based on subject's rankings for ABP 501 compared with adalimumab, and to assess trough serum concentration for ABP 501 compared with adalimumab.

Outcomes / endpoints

The primary efficacy endpoint was the risk ratio (RR) of ACR20 at week 24.

ACR20

To achieve an ACR20 response, at least 20% improvement compared to baseline was required for both swollen and tender joint counts (66/68 joint counts) and for at least 3 of the following 5 additional parameters:

- Subject's Global Health Assessment (on a 0 to 10 horizontal scale)
- Investigator's Global Health Assessment (on a 0 to 10 horizontal scale)
- subject's assessment of pain (on a 100-mm visual analogue scale [VAS])

- Health Assessment Questionnaire - Disability Index (HAQ-DI) (range: 0 to 3)
- serum CRP concentration

Secondary efficacy endpoints included the change from baseline of the Disease Activity Score 28-CRP (DAS28-CRP) at each time point (weeks 2, 4, 8, 12, 18, and 24); the RR of ACR20 responses at weeks 2 and 8; and the RR of ACR50 (50% improvement in ACR core set measurements) and ACR70 (70% improvement in ACR core set measurements) responses at week 24.

DAS28-CRP

The DAS28-CRP is a continuous scale based on 28 DAS joints from the ACR, the Subject's Global Health Assessment score (assessed as a score of 0 to 100 transformed from the results on a 0 to 10 horizontal scale by multiplying the horizontal scale by 10), and CRP, as follows: DAS28-CRP = 0.56*(TJC28)0.5 + 0.28*(SJC28)0.5 + 0.36*ln(CRP+1) + 0.014*GH + 0.96, where TJC28 is the tender joint count of the 28 joints in the DAS; SJC28 is the 28 swollen joint count; CRP is in mg/L; and GH is the Subject's Global Health Assessment on a 0 to 100 scale.

ACR50 and ACR70

The ACR50 and ACR70 are defined in a similar fashion to the ACR20, but require at least 50% and 70% improvement compared to baseline, respectively, for both swollen and tender joint counts, and for at least 3 out of 5 additional parameters (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, HAQ-DI, and CRP).

Sample size

Approximately 500 subjects were to be randomized in a 1:1 ratio to receive ABP 501 or adalimumab. This sample size was chosen to achieve > 90% power to demonstrate equivalence between the ABP 501 and adalimumab groups for the primary efficacy endpoint RR of ACR20 at week 24 (with a 2-sided significance level of 0.05, assuming an expected ACR20 response for both ABP 501 and adalimumab of 63% at week 24). Additional assumptions included an equivalence margin of (0.738, 1/0.738) and a 15% dropout by week 24.

This planned sample size was also expected to provide > 90% power to demonstrate equivalence between the ABP 501 and adalimumab groups for the secondary endpoint, change from baseline in DAS28-CRP with a 2-sided significance level of 0.05, assuming a standard deviation of 1.7 for both treatment groups, with an equivalence margin of ± 0.6 indicating the clinical equivalence between ABP 501 and adalimumab.

Randomisation

Subjects were randomized to receive either ABP 501 or adalimumab in a 1:1 ratio.

Randomization was stratified by geographic region (Eastern Europe, Western Europe, North America and Latin America) and prior biological use for RA (with prior biological use capped at 40% of the study population); for the statistical analyses, North America and Latin America were combined because of the low number of subjects that was enrolled in Latin America.

Blinding (masking)

During the study, subjects and all personnel involved with the conduct and the interpretation of the study were blinded to the subjects' randomized treatment assignment.

Statistical methods

Primary Efficacy Endpoint Analysis

The primary efficacy assessment evaluated the hypothesis that there were no clinically meaningful differences between the ABP 501 and adalimumab groups in the RR of ACR20 at week 24. The hypothesis was tested by comparing the 2-sided 90% CIs of the RR of the ACR20 at week 24 between the ABP 501 and adalimumab groups, estimated using a log-binomial regression model, with an equivalence margin of (0.738, 1/0.738). An inferential analysis was performed only for the primary endpoint. A sensitivity analysis of the equivalence test for primary endpoint, the RR of ACR20 at week 24, was also performed using the per-protocol analysis set.

The rationale for the equivalence margin was based on considerations in the draft US FDA *Non-inferiority Clinical Trials Guidance For Industry (2010)*. The equivalence margin of (0.738, 1/0.738) for the RR of ACR20 responses was chosen based on a published relevant adequate and well-controlled trial (Keystone et al, 2004).

In addition, a 95% CI of the RR of ACR20 between the ABP501 and adalimumab groups is displayed descriptively. The numbers and percentages of subjects meeting and not meeting the ACR20 are displayed by treatment group. The risk difference (RD) of ACR20 between the ABP 501 and adalimumab groups and corresponding 90% and 95% CIs are displayed descriptively.

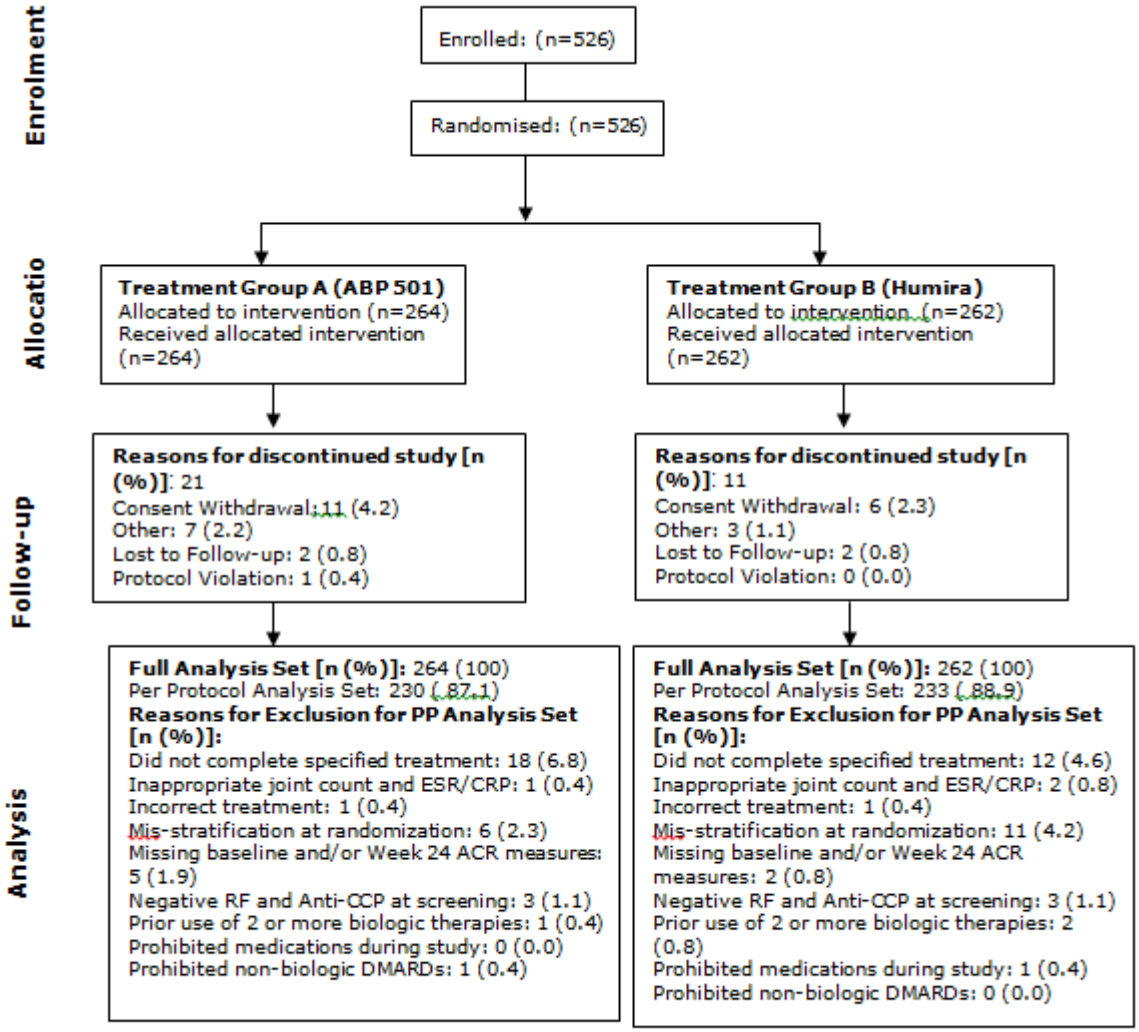
Secondary and Exploratory Efficacy Endpoint Analysis

The analyses on the secondary endpoints were considered descriptive. Treatment differences across assessed time points for the DAS28-CRP change from baseline were evaluated with a repeated-measures analysis. Besides stratification variables, visit (week), treatment group, treatment-by-visit interactions, and baseline DAS28-CRP were included in the model. The 90% and 95% CIs were constructed for mean difference of DAS28-CRP change from baseline between ABP 501 and adalimumab at each time point.

The RR and RD of ACR20 at weeks 2 and 8, and the RR and RD of ACR50 and ACR70 at week 24 were summarized descriptively by treatment group. Also, the corresponding 90% and 95% CIs for RR and RD are estimated using the generalized linear model adjusted for stratification factors.

Results

Participant flow



[1]All related to adverse events

Protocol violations:
A total of 55 of 526 subjects (10.5%) had 1 or more major protocol violations, and the incidence was similar in each group (see table below).

Major Protocol Violations by Treatment (Full Analysis Set)

Protocol Violation	ABP 501 (N = 264) n (%)	Adalimumab (N = 262) n (%)	Total (N = 526) n (%)
Total	25 (9.5)	30 (11.5)	55 (10.5)
Mis-stratification at randomization	6 (2.3)	11 (4.2)	17 (3.2)
Missing baseline and/or week 24 ACR measures	7 (2.7)	3 (1.1)	10 (1.9)
Prohibited medications during study	4 (1.5)	4 (1.5)	8 (1.5)
Negative RF and anti-CCP at screening	3 (1.1)	4 (1.5)	7 (1.3)
Inappropriate joint count and/or ESR/CRP	2 (0.8)	3 (1.1)	5 (1.0)
Prior use of ≥ 2 biological therapies	1 (0.4)	2 (0.8)	3 (0.6)
Prohibited non-biological DMARDs	1 (0.4)	2 (0.8)	3 (0.6)
Incorrect treatment	1 (0.4)	1 (0.4)	2 (0.4)
Positive PPD with positive quantiFERON®, symptoms of TB, or without adequate prophylaxis	0 (0.0)	2 (0.8)	2 (0.4)
IA, IV, or IM corticosteroids or IA hyaluronic acid injection	0 (0.0)	1 (0.4)	1 (0.2)
Informed consent not provided[a]	0 (0.0)	1 (0.4)	1 (0.2)

Recruitment

First Subject Enrolled: 24 October 2013
Last Subject Completed Study: 19 November 2014

Conduct of the study

Amendments to the Original Protocol

The original protocol dated 01 February 2013 was amended once on 06 June 2013. The primary endpoint was changed to RR of ACR20 at week 24 (assuming an expected ACR20 response for both ABP 501 and adalimumab of 63% at week 24) between ABP 501 and adalimumab. In addition the secondary efficacy criteria were changed and efficacy assessments at weeks 2, 8 and 18 were added.

This amendment was made before the first patient was enrolled.

Changes in Study Conduct

During the study, a printing error was discovered in the horizontal VAS that subjects used to assess pain at the injection site. All randomized subjects in the US sites assessed their pain at the injection site on a 95-mm horizontal VAS instead of a 100-mm scale. It was decided that all US sites were to continue to use the 95-mm VAS for current subjects and any new subjects enrolled. The 95-mm VAS was converted to a 100-mm VAS by multiplying the result on the 95-mm VAS by a factor of 100/95 and rounded to the nearest integer.

Protocol Violations

A total of 55 of 526 subjects (10.5%) had 1 or more major protocol violations, and the incidence was similar in each group (9.5% vs 11.5% in the ABP 501 and adalimumab groups respectively).

The most common major protocol violation was mis-stratification at randomization because of incorrect designation to prior biological use category. This occurred in 4.2% of subjects (11 of 262) in the adalimumab group and 2.3% of subjects (6 of 264) in the ABP 501 group. All other major protocol violations occurred in < 2% of subjects overall and were generally balanced across treatment groups

Baseline data

Table 13- Demographic and Baseline Characteristic by Treatment (Full Analysis Set)

Variable	ABP 501 (N = 264)	Adalimumab (N = 262)	Total (N = 526)
Sex - n (%)			
Women	214 (81.1)	212 (80.9)	426 (81.0)
Men	50 (18.9)	50 (19.1)	100 (19.0)
Ethnicity - n (%)			
Hispanic or Latino	33 (12.5)	25 (9.5)	58 (11.0)
Not Hispanic or Latino	230 (87.1)	236 (90.1)	466 (88.6)
Not allowed to collect	1 (0.4)	1 (0.4)	2 (0.4)
Race - n (%)			
White	251 (95.1)	249 (95.0)	500 (95.1)
Black or African American	9 (3.4)	12 (4.6)	21 (4.0)
Asian	3 (1.1)	0 (0.0)	3 (0.6)
Other	1 (0.4)	1 (0.4)	2 (0.4)
Age (Years)			
Mean (SD)	55.4 (11.88)	56.3 (11.47)	55.9 (11.67)
Median	57.0	58.0	57.0
Min, Max	22, 80	21, 77	21, 80
Weight (kg)			
Mean (SD)	74.85 (15.329)	76.85 (16.991)	75.85 (16.194)
Median	74.19	74.19	74.19
Min, Max	40.0, 121.3	41.0, 155.1	40.0, 155.1
Height (cm)			
Mean (SD)	164.07 (8.806)	165.81 (9.283)	164.94 (9.080)
Median	164.00	165.05	164.25
Min, Max	132.0, 190.0	130.8, 198.0	130.8, 198.0
BMI (kg/m^2)			
Mean (SD)	27.80 (5.296)	27.92 (5.570)	27.86 (5.429)
Median	27.18	27.30	27.25
Min, Max	16.1, 47.8	18.1, 54.4	16.1, 54.4

BMI = body mass index

More than 60% of subjects had a duration of RA ≥ 5 years (overall and for each treatment group), with a mean of 9.39 years and a median of 7.09 years since diagnosis. The subject proportions were similar between the ABP 501 and adalimumab group for positive RF status at screening: 92.0% versus 91.6%, respectively. The subject proportions were slightly lower in the ABP 501 group compared with the adalimumab group for both RF-positive and anti-CCP-positive status at screening: 73.5% versus 80.5%, respectively.

Table 14- Baseline Rheumatoid Arthritis Characteristics by Treatment (Full Analysis Set)

Variable	ABP 501 (N = 264)	Adalimumab (N = 262)	Total (N = 526)
Duration of RA (years)			
Mean (SD)	9.41 (8.076)	9.37 (8.047)	9.39 (8.054)
Median	7.22	7.05	7.09
Min, Max	0.3, 41.2	0.3, 42.0	0.3, 42.0
Duration of RA Category - n (%)			
<5 years	101 (38.3)	90 (34.4)	191 (36.3)
≥5 years	163 (61.7)	172 (65.6)	335 (63.7)
DAS28-CRP			
n	264	261	525
Mean (SD)	5.66 (0.918)	5.68 (0.911)	5.67 (0.914)
Median	5.59	5.70	5.60
Min, Max	3.2, 8.0	3.1, 7.9	3.1, 8.0
Swollen Joint Count			
Mean (SD)	14.7 (9.05)	14.1 (7.98)	14.4 (8.53)
Median	12.0	12.0	12.0
Min, Max	6, 66	1, 58	1, 66
Tender Joint Count			
Mean (SD)	24.3 (14.35)	23.9 (13.49)	24.1 (13.92)
Median	21.0	20.5	21.0
Min, Max	6, 68	6, 68	6, 68
Subject Global Health Assessment			
Mean (SD)	6.5 (1.92)	6.6 (1.86)	6.5 (1.89)
Median	7.0	7.0	7.0
Min, Max	1, 10	2, 10	1, 10
Investigator Global Health Assessment			
Mean (SD)	6.8 (1.29)	6.7 (1.59)	6.8 (1.45)
Median	7.0	7.0	7.0
Min, Max	3, 9	1, 10	1, 10
Subject's assessment of disease related pain			
Mean (SD)	58.3 (21.82)	60.6 (22.37)	59.5 (22.11)
Median	60.0	65.0	61.0
Min, Max	1, 100	2, 100	1, 100
HAQ-DI			
n	263	261	524
Mean (SD)	1.4819 (0.61715)	1.4976 (0.64743)	1.4897 (0.63186)
Median	1.5000	1.5000	1.5000
Min, Max	0.000, 3.000	0.000, 2.875	0.000, 3.000

Variable	ABP 501 (N = 264)	Adalimumab (N = 262)	Total (N = 526)
CRP (mg/L)			
Mean (SD)	13.881 (20.6870)	14.678 (19.3848)	14.278 (20.0338)
Median	6.140	7.630	7.030
Min, Max	0.12, 222.10	0.12, 147.41	0.12, 222.10
RF Status at Screening - n (%)			
Positive	243 (92.0)	240 (91.6)	483 (91.8)
Negative	20 (7.6)	22 (8.4)	42 (8.0)
Anti-CCP Status at Screening - n (%)			
Positive	212 (80.3)	230 (87.8)	442 (84.0)
Negative	48 (18.2)	30 (11.5)	78 (14.8)
RF and anti-CCP Status at Screening - n (%)			
RF positive and anti-CCP positive	194 (73.5)	211 (80.5)	405 (77.0)
RF positive and anti-CCP negative	45 (17.0)	27 (10.3)	72 (13.7)
RF negative and anti-CCP positive	17 (6.4)	19 (7.3)	36 (6.8)
RF negative and anti-CCP negative	3 (1.1)	3 (1.1)	6 (1.1)

CCP = cyclic citrullinated peptide; CRP = C-reactive protein; DAS28-CRP = Disease Activity Score 28-C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; RA = rheumatoid arthritis; RF= rheumatoid factor

Table 15- Baseline Rheumatoid Arthritis Medications by Treatment (Full Analysis Set)

Variable	ABP 501 (N = 264)	Adalimumab (N = 262)	Total (N = 526)
Prior Biological Use for RA - n (%)			
Yes	71 (26.9)	74 (28.2)	145 (27.6)
No	193 (73.1)	188 (71.8)	381 (72.4)
Oral Corticosteroids - n (%)			
Yes	134 (50.8)	130 (49.6)	264 (50.2)
No	130 (49.2)	132 (50.4)	262 (49.8)
NSAIDs - n (%)			
Yes	159 (60.2)	168 (64.1)	327 (62.2)
No	105 (39.8)	94 (35.9)	199 (37.8)
Methotrexate Dose (mg/week)			
n	263[a]	262	525
Mean (SD)	16.89 (4.811)	16.56 (4.932)	16.72 (4.870)
Median	15.00	15.00	15.00
Min, Max	7.5, 25.0	7.5, 25.0	7.5, 25.0

NSAIDs = nonsteroidal anti-inflammatory drugs

[a] One subject was not on a stable dose of methotrexate and was excluded from the per-protocol analysis set because the subject also had a negative result for RF and anti-CCP at screening (Listing 16-2.2).

Demographic and baseline characteristics were reasonably balanced between the treatment groups. More patients in the adalimumab group were CCP positive (87% vs 80%). CCP-antibodies indicate a more progressive disease. The majority of subjects were white women.

Numbers analysed

Table 16- Subject Populations by Treatment (All Randomized Subjects)

Population	ABP 501 (N = 264)	Adalimumab (N = 262)	Total (N = 526)
Subjects Randomized[a] [n]	264	262	526
Subjects Treated[ab] [n (%)]	264 (100.0)	262 (100.0)	526 (100.0)
Subjects Randomized but Not Treated[ab] [n (%)]	0 (0.0)	0 (0.0)	0 (0.0)
Full Analysis Set[abc] [n (%)]	264 (100.0)	262 (100.0)	526 (100.0)
Per-protocol (PP) Analysis Set[bd] [n (%)]	230 (87.1)	233 (88.9)	463 (88.0)

[a] Based on treatment subject randomized to.
[b] % = Percent of all randomized subjects.
[c] Full Analysis Set (FAS): All subjects randomized in the study, with treatment assignment based on randomized treatment.
[d] Per Protocol Analysis Set (PP): All randomized subjects who have completed the specified treatment period and did not experience a protocol deviation that affects their evaluation for primary objective of the study. Subjects are summarized according to their actual treatment received.

The full analysis set, which consisted of all 526 subjects who were randomized in this study, was used for the efficacy analysis set. The per-protocol analysis set was used as a sensitivity analysis for selected key efficacy endpoints.

Outcomes and estimation

Primary Endpoint

ACR20 at Week 24

Table 17- Analysis of ACR20 at Week 24 by Treatment (Full Analysis Set with Last Observation Carried Forward Imputation)

Category	ABP 501 (N = 264)	Adalimumab (N = 262)
ACR20 Responder - n/N1 (%)	194/260 (74.6)	189/261 (72.4)
ACR20 Non-responder - n/N1 (%)	66/260 (25.4)	72/261 (27.6)
Risk Ratio of ACR20[a]	1.039	
90% CI for Risk Ratio of ACR20[a]	(0.954, 1.133)	
95% CI for Risk Ratio of ACR20[a]	(0.938, 1.152)	
Risk Difference of ACR20 (%)[a]	2.604	
90% CI for Risk Difference of ACR20 (%)[a]	(-3.728, 8.936)	
95% CI for Risk Difference of ACR20 (%)[a]	(-4.941, 10.149)	

ACR20 = 20% improvement in the American College of Rheumatology core set measurements;
CI = confidence interval; n = number of subjects meeting the criteria at the visit; N1 = number of subjects who were randomized and had an assessment at the visit.
a Based on a generalized linear model adjusted for geographic region and prior biological use for RA as covariates in the model.

At week 24, 74.6% of subjects (194 of 260) in the ABP 501 group and 72.4% of subjects (189 of 261) in the adalimumab group met the ACR20 response criteria (Table 32 above). The RR of ACR20 for ABP 501 versus adalimumab was 1.039 with the 2-sided 95% CI of RR (0.938, 1.152).

Sensitivity Analyses for ACR20 at Week 24

The sensitivity analysis for the primary efficacy endpoint includes the full analysis set using non-responders imputation. Results for this sensitivity analysis showed that at week 24, 71.2% of subjects

(188 of 264) in the ABP 501 group and 72.1% of subjects (189 of 262) in the adalimumab group met the ACR20 response criteria. Based on the non-responder imputation analysis, the RR of ACR20 for ABP 501 versus adalimumab was 1.000 with the 2-sided 95% CI of RR of ACR20 for ABP 501 versus adalimumab (0.899, 1.113) confirming the clinical equivalence between ABP 501 and adalimumab.

In the Per Protocol analysis set (n=230 in the ABP group, n=233 in the adalimumab group), 76.5% vs 76.4% met the ACR20 response criteria at week 24. The RR for ABP 501 vs adalimumab was 1.009 (95% CI 0.912, 1.115).

The week 24 ACR20 results from other sensitivity analyses (full analysis set using observed values, per-protocol analysis set, full analysis set using the LOCF for actual treatment received, analysis based on backward model selection for the full analysis set using the LOCF, and repeated-measures analysis using full analysis set with observed values) were also similar to the results of the primary efficacy analysis (using the LOCF).

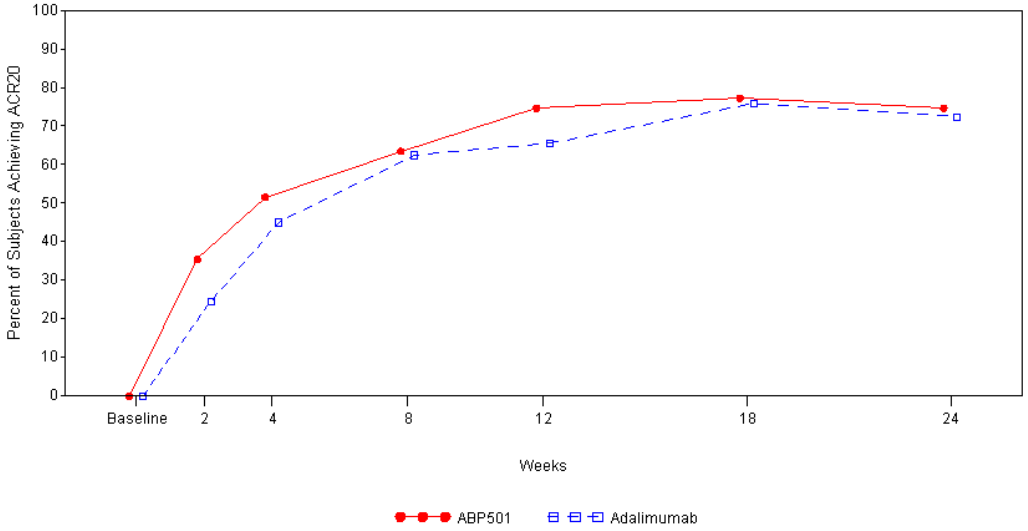
Secondary Efficacy Endpoints

ACR20 at Weeks 2 and 8

At week 2, 35.4% of subjects (90 of 254) in the ABP 501 group and 24.5% of subjects (63 of 257) in the adalimumab group met the ACR20 response criteria. The RR of ACR20 for ABP 501 versus adalimumab was 1.421 with the 2-sided 95% CI of (1.086, 1.860). The RD of ACR20 for ABP 501 versus adalimumab was 11.038% with the 2-sided 95% CI of (3.265%, 18.812%).

At week 8, 63.5% of subjects (165 of 260) in the ABP 501 group and 62.5% of subjects (163 of 261) in the adalimumab group met the ACR20 response criteria. The RR of ACR20 for ABP 501 versus adalimumab was 1.015 with the 2-sided 95% CI of (0.889, 1.158). The RD of ACR20 for ABP 501 versus adalimumab was 0.973% with the 2-sided 95% CI of (-7.324%, 9.269%).

Figure 2-Percent of Subjects Achieving ACR20 by Treatment (Full Analysis Set With Last Observation Carried Forward



The point estimates and CI for RR at the remaining visits are presented below.

Table 18-Analysis of ACR20 by Visit and Treatment (Study 20120262 Full Analysis Set, LOCF)

Time Point	ABP 501 (N = 264)	Adalimumab (N = 262)
Week 2		
ACR20 responder [n/N1 (%)]	90/254 (35.4)	63/257 (24.5)
Risk ratio ACR20[a]	1.421	
90% CI for risk ratio ACR20[a]	(1.134, 1.781)	
95% CI for risk ratio ACR20[a]	(1.086, 1.860)	
Risk difference ACR20 (%)[a]	11.038	
90% CI for risk difference ACR20 (%)[a]	(4.515, 17.562)	
95% CI for risk difference ACR20 (%)[a]	(3.265, 18.812)	
Week 4		
ACR20 responder [n/N1 (%)]	134/260 (51.5)	117/260 (45.0)
Risk ratio ACR20[a]	1.157	
90% CI for risk ratio ACR20[a]	(0.996, 1.343)	
95% CI for risk ratio ACR20[a]	(0.968, 1.382)	
Risk difference ACR20 (%)[a]	6.495	
90% CI for risk difference ACR20 (%)[a]	(-0.678, 13.668)	
95% CI for risk difference ACR20 (%)[a]	(-2.052, 15.042)	
Week 8		
ACR20 responder [n/N1 (%)]	165/260 (63.5)	163/261 (62.5)
Risk ratio ACR20[a]	1.015	
90% CI for risk ratio ACR20[a]	(0.908, 1.134)	
95% CI for risk ratio ACR20[a]	(0.889, 1.158)	
Risk difference ACR20 (%)[a]	0.973	
90% CI for risk difference ACR20 (%)[a]	(-5.990, 7.935)	
95% CI for risk difference ACR20 (%)[a]	(-7.324, 9.269)	
Week 12		
ACR20 responder [n/N1 (%)]	194/260 (74.6)	171/261 (65.5)
Risk ratio ACR20[a]	1.138	
90% CI for risk ratio ACR20[a]	(1.035, 1.250)	
95% CI for risk ratio ACR20[a]	(1.016, 1.273)	
Risk difference ACR20 (%)[a]	9.054	
90% CI for risk difference ACR20 (%)[a]	(2.502, 15.605)	
95% CI for risk difference ACR20 (%)[a]	(1.247, 16.861)	

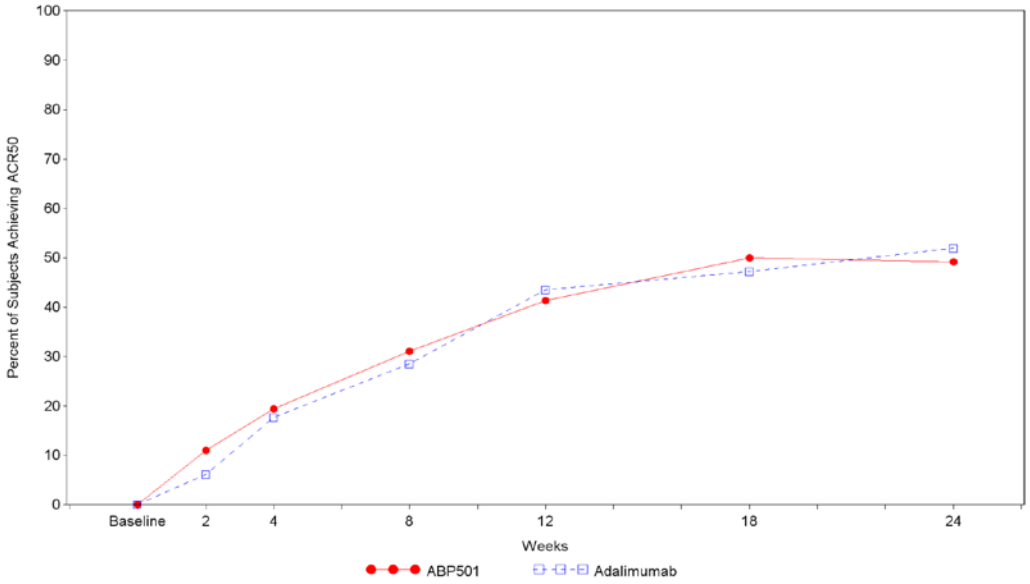
Time Point	ABP 501 (N = 264)	Adalimumab (N = 262)
Week 18		
ACR20 responder [n/N1 (%)]	201/260 (77.3)	198/261 (75.9)
Risk ratio ACR20[a]	1.023	
90% CI for risk ratio ACR20[a]	(0.945, 1.108)	
95% CI for risk ratio ACR20[a]	(0.931, 1.125)	
Risk difference ACR20 (%)[a]	1.670	
90% CI for risk difference ACR20[a]	(-4.422, 7.761)	
95% CI for risk difference ACR20 (%)[a]	(-5.589, 8.928)	

ACR20 = 20% improvement in American College of Rheumatology core set measurements; CI = confidence interval; CSR = clinical study report; LOCF = last observation carried forward; n = number of subjects meeting the criteria at the visit; N1 = number of subjects who were randomized and had an assessment at the visit.
a Based on a generalized linear model adjusted for geographic region and prior biologic use as covariates in the model.

ACR50

At week 24, 49.2% of subjects (120 of 244) in the ABP 501 group and 52.0% of subjects (131 of 252) in the adalimumab group met the ACR50 response criteria. The RR of ACR50 for ABP 501 versus adalimumab was 0.948 with the 2-sided 95% CI of (0.796, 1.128). The RD of ACR50 for ABP 501 versus adalimumab was -2.836% with the 2-sided 90% CI of (-10.220%, 4.547%) and the 2-sided 95% CI of (-11.634%, 5.961%).

Figure 3-Percent of Subjects Achieving ACR50 (Study 20120262 Full Analysis Set as Observed)



In contrast to the ACR20 results, for ACR50, the difference at week 2 was not significant, although the point estimate was high (RR 1.7). At week 12, the difference was in favour of adalimumab.

Table 19- Analysis of ACR50 by Visit and Treatment (Full Analysis Set as Observed)

Time Point	ABP 501 (N = 264)	Adalimumab (N = 262)
Week 2		
ACR50 responder [n/N1 (%)]	28/255 (11.0)	16/257 (6.2)
Risk ratio ACR50[a]	1.766	
90% CI for risk ratio ACR50[a]	(1.080, 2.887)	
95% CI for risk ratio ACR50[a]	(0.983, 3.172)	
Risk difference ACR50 (%)[a]	3.740	
90% CI for risk difference ACR50 (%)[a]	(-0.839, 8.319)	
95% CI for risk difference ACR50 (%)[a]	(-1.716, 9.196)	
Week 4		
ACR50 responder [n/N1 (%)]	50/257 (19.5)	46/259 (17.8)
Risk ratio ACR50[a]	1.089	
90% CI for risk ratio ACR50[a]	(0.806, 1.473)	
95% CI for risk ratio ACR50[a]	(0.760, 1.561)	
Risk difference ACR50 (%)[a]	1.466	
90% CI for risk difference ACR50 (%)[a]	(-4.091, 7.024)	
95% CI for risk difference ACR50 (%)[a]	(-5.155, 8.088)	
Week 8		
ACR50 responder [n/N1 (%)]	78/251 (31.1)	73/256 (28.5)
Risk ratio ACR50[a]	1.089	
90% CI for risk ratio ACR50[a]	(0.871, 1.362)	
95% CI for risk ratio ACR50[a]	(0.835, 1.421)	
Risk difference ACR50 (%)[a]	2.543	
90% CI for risk difference ACR50 (%)[a]	(-4.083, 9.169)	
95% CI for risk difference ACR50 (%)[a]	(-5.352, 10.438)	
Week 12		
ACR50 responder [n/N1 (%)]	102/247 (41.3)	111/255 (43.5)
Risk ratio ACR50[a]	0.946	
90% CI for risk ratio ACR50[a]	(0.797, 1.123)	
95% CI for risk ratio ACR50[a]	(0.771, 1.160)	
Risk difference ACR50 (%)[a]	-2.151	
90% CI for risk difference ACR50 (%)[a]	(-9.402, 5.100)	
95% CI for risk difference ACR50 (%)[a]	(-10.791, 6.489)	

Time Point	ABP 501 (N = 264)	Adalimumab (N = 262)
Week 18		
ACR50 responder [n/N1 (%)]	123/246 (50.0)	120/254 (47.2)
Risk ratio ACR50[a]	1.060	
90% CI for risk ratio ACR50[a]	(0.911, 1.233)	
95% CI for risk ratio ACR50[a]	(0.885, 1.270)	
Risk difference ACR50 (%)[a]	2.779	
90% CI for risk difference ACR50 (%)[a]	(-4.571, 10.128)	
95% CI for risk difference ACR50 (%)[a]	(-5.978, 11.536)	
Week 24		
ACR50 responder [n/N1 (%)]	120/244 (49.2)	131/252 (52.0)
Risk ratio ACR50[a]	0.948	
90% CI for risk ratio ACR50[a]	(0.819, 1.097)	
95% CI for risk ratio ACR50[a]	(0.796, 1.128)	
Risk difference ACR50 (%)[a]	-2.836	
90% CI for risk difference ACR50 (%)[a]	(-10.220, 4.547)	
95% CI for risk difference ACR50 (%)[a]	(-11.634, 5.961)	

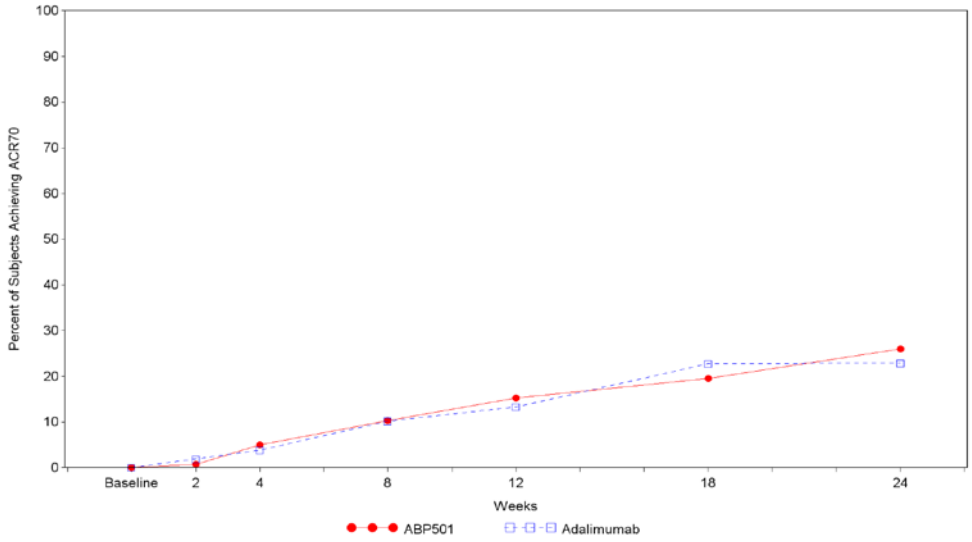
ACR50 = 50% improvement in American College of Rheumatology core set measurements; CI = confidence interval; CSR = clinical study report; n = number of subjects meeting the criteria at the visit; N1 = number of subjects who were randomized and had an assessment at the visit.

a Based on a generalized linear model adjusted for geographic region and prior biologic use as covariates in the model.

ACR70

At week 24, 26.0% of subjects (64 of 246) in the ABP 501 group and 22.9% of subjects (58 of 253) in the adalimumab group met the ACR70 response criteria. The RR of ACR70 for ABP 501 versus adalimumab was 1.130 with the 2-sided 95% CI of (0.830, 1.538). The RD of ACR20 for ABP 501 versus adalimumab was 3.147% with the 2-sided 95% CI of (-4.388%, 10.681%).

Figure 4-Percent of Subjects Achieving ACR70 (Study 20120262 Full Analysis Set as Observed)



For ACR70 response, no statistically significant differences were seen and the point estimates of RR and RD were low.

Disease Activity Score 28 CRP Change From Baseline

At week 24, the difference between treatment groups in the mean change from baseline in DAS28-CRP was -0.01 with a 2-sided 95% CI of (-0.22, 0.20) (Table 36). The 95% CI fell within the predefined equivalence margin of (-0.6, 0.6).

Table 20-Analysis of DAS28-CRP Change From Baseline by Visit (Study 20120262 Full Analysis Set as Observed)

Time Point	ABP 501 (N = 264)	Adalimumab (N = 262)
Week 2 (n)	254	252
Mean (SD)	-1.01 (0.891)	-0.96 (0.890)
Difference between means[a]	-0.05	
90% CI for difference between means[a]	(-0.18, 0.08)	
95% CI for difference between means[a]	(-0.20, 0.10)	
Week 4 (n)	255	254
Mean (SD)	-1.45 (1.048)	-1.42 (0.979)
Difference between means[a]	-0.02	
90% CI for difference between means[a]	(-0.17, 0.12)	
95% CI for difference between means[a]	(-0.20, 0.15)	
Week 8 (n)	247	255
Mean (SD)	-1.79 (1.075)	-1.70 (1.093)
Difference between means[a]	-0.08	
90% CI for difference between means[a]	(-0.24, 0.08)	
95% CI for difference between means[a]	(-0.27, 0.11)	

Week 12 (n)	245	250
Mean (SD)	-2.04 (1.112)	-1.93 (1.171)
Difference between means[a]	-0.09	
90% CI for difference between means[a]	(-0.26, 0.07)	
95% CI for difference between means[a]	(-0.29, 0.10)	
Week 18 (n)	244	250
Mean (SD)	-2.30 (1.184)	-2.17 (1.189)
Difference between means[a]	-0.09	
90% CI for difference between means[a]	(-0.25, 0.08)	
95% CI for difference between means[a]	(-0.29, 0.12)	
Time Point	ABP 501 (N = 264)	Adalimumab (N = 262)
Week 24 (n)	243	250
Mean (SD)	-2.32 (1.237)	-2.32 (1.209)
Difference between means[a]	-0.01	
90% CI for difference between means[a]	(-0.18, 0.17)	
95% CI for difference between means[a]	(-0.22, 0.20)	

Note: The unstructured covariance structure was used in the model.
CI = confidence interval; CSR = clinical study report; DAS28-CRP = Disease Activity Score 28 – C-reactive protein; SD = standard deviation.
[a] Difference between means, 90% and 95% CIs for difference between means is based on repeated-measures analysis with the DAS28-CRP change from baseline as the response and the stratification variables, visit, treatment, treatment-by-visit interaction, and the baseline DAS28-CRP measurement as predicators in the model.

The maximum difference of mean change between groups was 0.09 with 95% CI (-0.29, 0.12) at Week 18.

Ancillary analysis

ACR Individual Components

No clinically meaningful differences in the observed values or in the percent improvement over time of ACR individual components (Subject's Assessment of Disease-related Pain; HAQ-DI Total Score; CRP (mg/L) Concentration) between ABP 501 and Humira were reported.

DAS28-CRP Remission

Proportionally more subjects in the adalimumab group achieved remission compared with the ABP 501 group from week 2 to week 18. At week 24, approximately one-third of subjects in each treatment group had achieved full DAS28-CRP remission. At week 24, 74/243 (30.5%) in the ABP 501 treated group and 89/251 (35.5%) in the adalimumab-treated group achieved DAS28-CRP remission. The RR was 0.853, with 95% CI (0.662, 1.099).The Risk Difference was -4.954%, 95% CI (-13.237%, 3.330%). At earlier time points, the opposite was seen, i.e. higher proportions achieving DAS28-CRP remission in the ABP 501-treated group.

Exploratory Efficacy Endpoint

Subject Injection Site Pain Perception Assessment

Mean injection site pain rating scores were lower in the ABP 501 group (range: 10.0 to 10.7 mm) compared with the adalimumab group (range: 16.1 to 21.4 mm) at each study visit. Some subjects had no pain (0 mm) whereas others had the highest possible pain (100 mm). Mean pain scores were similar across all study weeks in the ABP 501 group (range: 10.0 to 10.7 mm). However, mean pain scores tended to slightly decrease over time in the adalimumab group, from 21.4 mm at baseline to 16.1 mm at week 12. Similar results were reported using a sensitivity analysis that excluded subjects who used the 95-mm VAS scale (see section "conduct of the study" above).

Immunogenicity

- Positive post-baseline **binding ADA** incidence: 38.3% and 38.2% for the ABP 501 and Humira groups, respectively with a difference in the incidence of 0.219% (90% CI: [-6.795%, 7.234%]).
- Positive post-baseline **neutralizing** ADAs incidence: 9.1% and 11.1% for the ABP 501 and Humira groups, respectively with a difference in the incidence of -1.434% (90% CI: [-6.741%, 3.874%]).

Table 21-Analysis of ACR20 by Neutralizing Anti-drug Antibodies Status Subgroup (Full Analysis Set with LOCF)

Anti-drug Antibodies Status - On-study Positive Timepoint	ABP 501 (N = 24)	Adalimumab (N = 29)
Week 24		
ACR20 Responder [n/N1 (%)]	16/24 (66.7)	21/29 (72.4)
ACR20 Non-Responder [n/N1 (%)]	8/24 (33.3)	8/29 (27.6)
Risk Ratio of ACR20[a]	-	
90% CI for Risk Ratio of ACR20[a]	-	
95% CI for Risk Ratio of ACR20[a]	-	
Risk Difference of ACR20 (%)[a]	-11.073	
90% CI for Risk Difference of ACR20 (%)[a]	(-35.355, 13.208)	
95% CI for Risk Difference of ACR20 (%)[a]	(-40.006, 17.860)	

Note: n = Number of subjects meeting the criteria at the visit. N1 = Number of subjects who were randomized and had an assessment at the visit.
[a] Based on a generalized linear model adjusted for geographic region and prior biologic use for RA as covariates in the model. The risk differences and its confidence intervals at week 4 and 24, and the risk ratio and its confidence intervals at week 18 for the group of Anti-drug Antibodies Status - On-study Positive were estimated from the generalized liner model with relative Hessian convergence criterion greater than the default limit of 0.0001.
- Not available because the generalized liner model was not converged.

A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of ABP 501 Compared with Adalimumab in Subjects with Moderate to Severe Plaque Psoriasis

Methods

Study Participants

Eligible subjects met the following key criteria:

- Subject was ≥ 18 and ≤ 75 years of age at time of screening. Subject had stable moderate to severe plaque psoriasis for at least 6 months.
- Subject had involved BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and baseline.

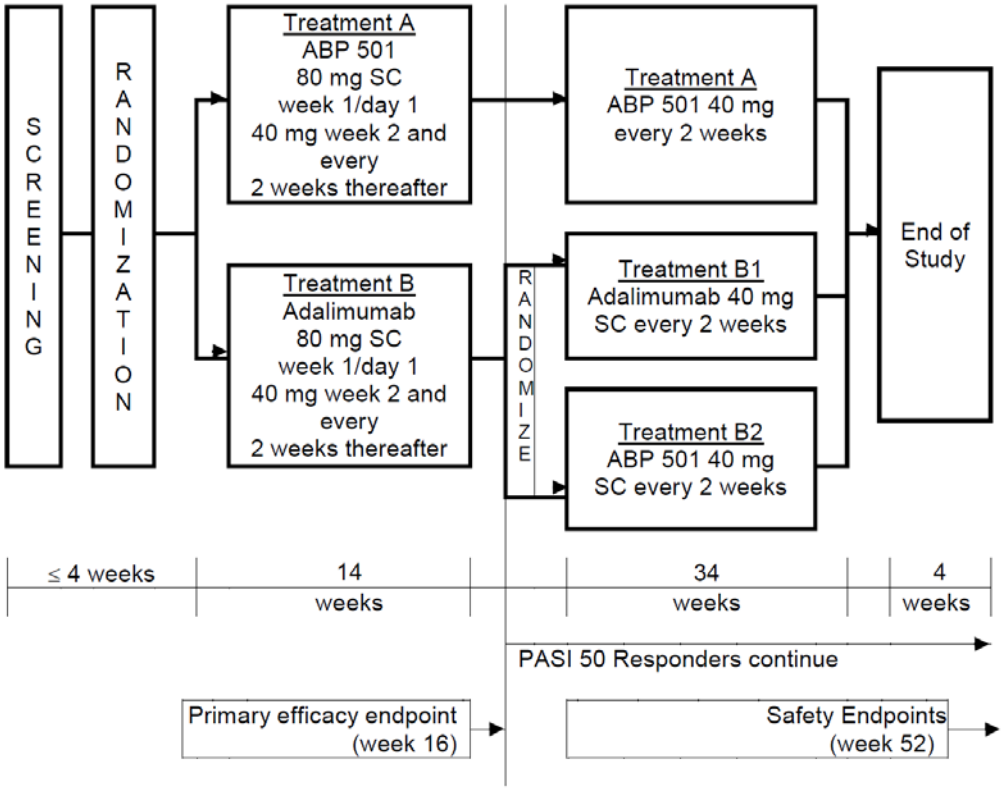
- Subject was a candidate for systemic therapy or phototherapy.
- Subject had previously failed, had an inadequate response, intolerance to, or contraindication to at least 1 conventional anti-psoriatic systemic therapy (eg, methotrexate, cyclosporine, psoralen plus ultraviolet light A).

Key exclusion criteria included subjects with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at screening that would interfere with evaluations of the effect of IP on psoriasis; and prior use of 2 or more biologics for treatment of psoriasis, adalimumab, or a biosimilar of adalimumab.

This study was conducted at 49 centres in 6 countries (Australia, Canada, France, Germany, Hungary, and Poland).

Treatments

Figure 5-Study Diagram study 20120263



PASI = Psoriasis Area and Severity Index; SC = subcutaneous

Objectives

The primary study objective was to evaluate the efficacy of ABP 501 in subjects with moderate to severe plaque psoriasis, as measured by the Psoriasis Area and Severity Index (PASI) percent improvement from baseline, compared with Humira.

The secondary study objectives were to assess the safety and immunogenicity of ABP 501 compared with Humira and to assess efficacy in terms of PASI 75 response (75% or greater improvement from baseline in PASI score), static Physician's Global Assessment (sPGA), and percent body surface area (BSA) affected.

Moreover, the exploratory objectives were to assess the perception of injection site pain based on subjects' rankings for ABP 501 compared with Humira injections.

Outcomes/endpoints

The Primary efficacy endpoint was PASI percent improvement from baseline at week 16.

PASI score

The PASI score is a measure of the average redness (erythema), thickness (induration), and scaliness (scaling), each graded on a 0 to 4 scale of the lesions, weighted by the area of involvement in the 4 main body areas (head and neck, trunk, upper extremities, and lower extremities) (Feldman and Krueger, 2005). A higher PASI score indicates greater severity and/or more extensive psoriasis.

Secondary efficacy endpoints included PASI percent improvement from baseline to weeks 32 and 50; PASI 75 responses at weeks 16, 32, and 50; Static Physician's Global Assessment (PGA) responses at weeks 16, 32 and 50, and body surface area (BSA) involvement at weeks 16, 32, and 50 .

sPGA

The sPGA is a 6-point scale used to measure the severity of disease (induration, scaling, and erythema).

BSA

BSA an estimate made by assuming that the subject's palm, excluding the fingers and thumb, represents roughly 1% of the body's surface area.

An additional efficacy analysis defined in the SAP was PASI 50 response at weeks 16, 32, and 50.

Subject assessment of pain at the injection site was an exploratory endpoint. The subject's assessment of pain immediately after injection of ABP 501 or adalimumab was measured using a horizontal visual analog scale (VAS), with extremes ranging from "no pain at all" (0 on the scale) to "a lot of pain" (100 on the scale).

Sample size

Approximately 340 subjects (170 subjects per treatment group) were to be enrolled. This sample size was chosen to provide > 90% power to demonstrate equivalence at a significance level of 0.025 on the primary endpoint of PASI percent improvement from baseline at week 16 with margins of (-15, 15).

Randomisation

Randomization was stratified by geographic region (Eastern Europe, Western Europe, "Other" [Australia and Canada]) and prior biologic use for Ps (yes/no, with prior biologic use capped at 50% of the study population). Eligible subjects who continued treatment beyond week 16 were re-randomized in a blinded fashion as described above. Subjects without a PASI 50 or better response within the week 16 visit window were discontinued from the study.

Blinding (masking)

Double-blind study.

Statistical methods

Primary Analysis

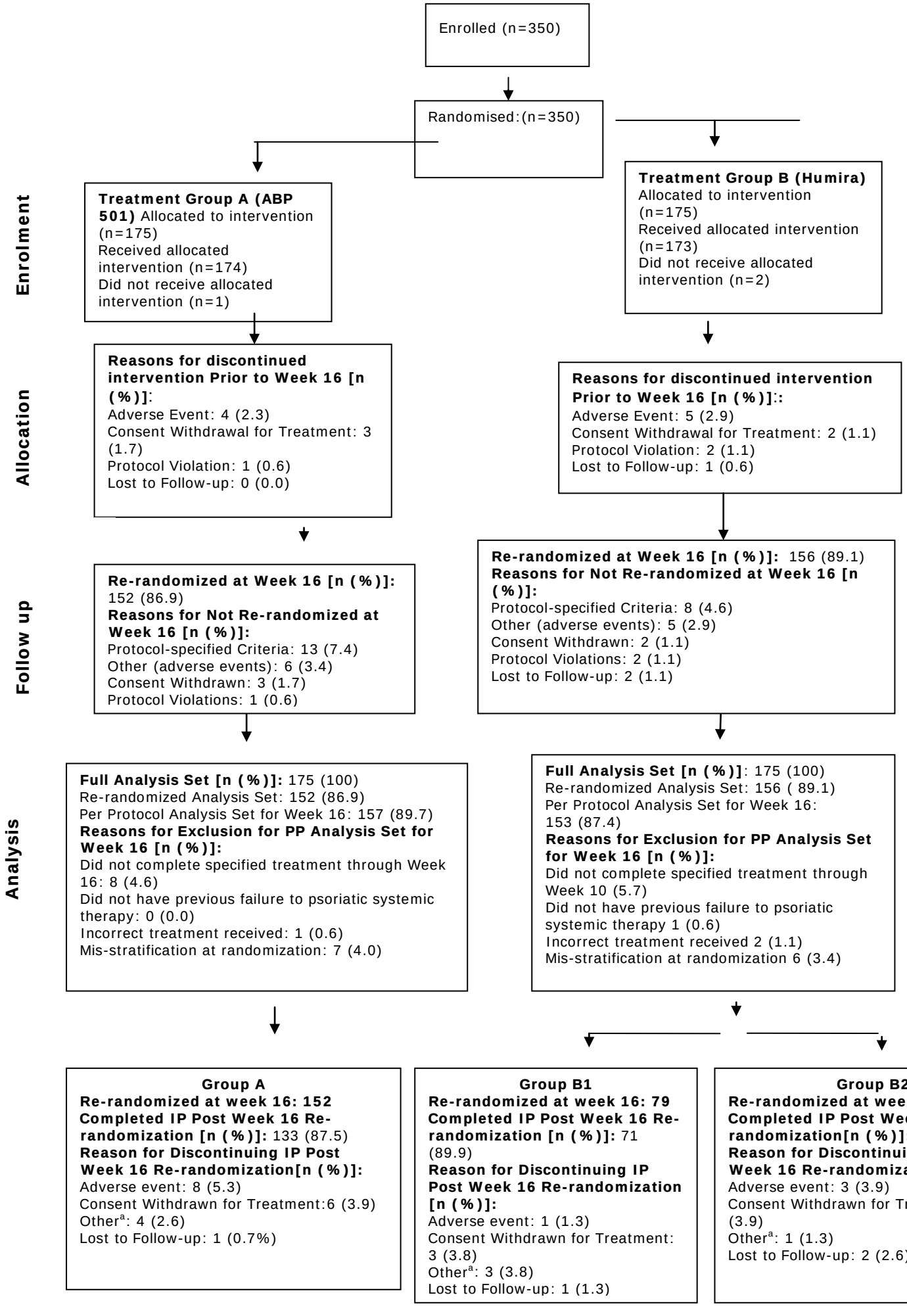
The primary efficacy endpoint, PASI percent improvement from baseline at week 16, was analyzed using the full analysis set with missing values imputed using the last observation carried forward (LOCF) method. Clinical equivalence of the primary endpoint was evaluated by comparing the 2-sided 95% confidence interval (CI) of the difference of PASI percent improvement from baseline to week 16 between Treatment A (ABP 501) and Treatment B (adalimumab) with an equivalence margin of (-15, 15). The 2-sided 95% CI of the group difference was estimated using an ANCOVA model with baseline PASI score and stratification factors (geographic region and prior biologic use for psoriasis) as covariates. The PASI percent improvement was summarized descriptively for all measured timepoints. The 95% and 90% CIs for the difference of treatments were presented descriptively.

Sensitivity Analyses

To assess the robustness of the primary PASI percent improvement from baseline results, the primary analysis was repeated using the full analysis set based on observed cases and per-protocol analysis set based on observed cases. Another sensitivity analysis was done to explore the impact of the following covariates relative to PASI percent improvement at week 16 in addition to the randomization stratification factors: age group (< 65 years and ≥ 65 years), race, sex, disease duration (< 5 years and ≥ 5 years), neutralizing antidrug antibody status, concomitant topical steroid use, and prior use of systemic or phototherapies. All the covariates were to be included in the model, and backwards model selection was used to determine if any of the listed covariates had an impact on the primary efficacy endpoint at the significance of 0.10. The model maintained treatment, baseline PASI score, and the stratification factors regardless. This sensitivity analysis used the full analysis set with LOCF imputation. For each subgroup of stratification factors, age group (< 65 years and ≥ 65 years), race, sex, disease duration group (< 5 years and ≥ 5 years), neutralizing antidrug antibody status, concomitant topical steroid use, and prior use of systemic or phototherapies, the PASI percent improvement at weeks 4, 8, 12, and 16 was also examined in the subgroups descriptively. This sensitivity analysis used the full analysis set with LOCF imputation. PASI percent improvement was also analyzed based on a repeated measures analysis, where data from all assessed timepoints through the week 16 visit were included as observed for the full analysis set. In addition to stratification variables and baseline PASI score, visit week (as a categorical variable), treatment, and treatment-by-visit interaction were included in this mixed model repeated measures analysis.

Results

Participant flow


Enrolment
Allocation
Follow up
Analysis
Enrolled (n=350)
Randomised:(n=350)
Treatment Group A (ABP 501) Allocated to intervention (n=175)
Received allocated intervention (n=174)
Did not receive allocated intervention (n=1)
Treatment Group B (Humira)
Allocated to intervention (n=175)
Received allocated intervention (n=173)
Did not receive allocated intervention (n=2)
Reasons for discontinued intervention Prior to Week 16 [n (%)]:
Adverse Event: 4 (2.3)
Consent Withdrawal for Treatment: 3 (1.7)
Protocol Violation: 1 (0.6)
Lost to Follow-up: 0 (0.0)
Reasons for discontinued intervention Prior to Week 16 [n (%)]::
Adverse Event: 5 (2.9)
Consent Withdrawal for Treatment: 2 (1.1)
Protocol Violation: 2 (1.1)
Lost to Follow-up: 1 (0.6)
Re-randomized at Week 16 [n (%)]: 152 (86.9)
Reasons for Not Re-randomized at Week 16 [n (%)]:
Protocol-specified Criteria: 13 (7.4)
Other (adverse events): 6 (3.4)
Consent Withdrawn: 3 (1.7)
Protocol Violations: 1 (0.6)
Re-randomized at Week 16 [n (%)]: 156 (89.1)
Reasons for Not Re-randomized at Week 16 [n (%)]:
Protocol-specified Criteria: 8 (4.6)
Other (adverse events): 5 (2.9)
Consent Withdrawn: 2 (1.1)
Protocol Violations: 2 (1.1)
Lost to Follow-up: 2 (1.1)
Full Analysis Set [n (%)]: 175 (100)
Re-randomized Analysis Set: 152 (86.9)
Per Protocol Analysis Set for Week 16: 157 (89.7)
Reasons for Exclusion for PP Analysis Set for Week 16 [n (%)]:
Did not complete specified treatment through Week 16: 8 (4.6)
Did not have previous failure to psoriatic systemic therapy: 0 (0.0)
Incorrect treatment received: 1 (0.6)
Mis-stratification at randomization: 7 (4.0)
Full Analysis Set [n (%)]: 175 (100)
Re-randomized Analysis Set: 156 (89.1)
Per Protocol Analysis Set for Week 16: 153 (87.4)
Reasons for Exclusion for PP Analysis Set for Week 16 [n (%)]:
Did not complete specified treatment through Week 10 (5.7)
Did not have previous failure to psoriatic systemic therapy 1 (0.6)
Incorrect treatment received 2 (1.1)
Mis-stratification at randomization 6 (3.4)
Group A
Re-randomized at week 16: 152
Completed IP Post Week 16 Re-randomization [n (%)]: 133 (87.5)
Reason for Discontinuing IP Post Week 16 Re-randomization[n (%)]:
Adverse event: 8 (5.3)
Consent Withdrawn for Treatment:6 (3.9)
Other[a]: 4 (2.6)
Lost to Follow-up: 1 (0.7%)
Group B1
Re-randomized at week 16: 79
Completed IP Post Week 16 Re-randomization [n (%)]: 71 (89.9)
Reason for Discontinuing IP Post Week 16 Re-randomization [n (%)]:
Adverse event: 1 (1.3)
Consent Withdrawn for Treatment: 3 (3.8)
Other[a]: 3 (3.8)
Lost to Follow-up: 1 (1.3)
Group B2
Re-randomized at week 16: 77
Completed IP Post Week 16 Re-randomization[n (%)]: 68 (88.3)
Reason for Discontinuing IP Post Week 16 Re-randomization [n (%)]
Adverse event: 3 (3.9)
Consent Withdrawn for Treatment: 3 (3.9)
Other[a]: 1 (1.3)
Lost to Follow-up: 2 (2.6)

IP = investigational product
a Subjects discontinued investigational product because of lack of efficacy (6 subjects), noncompliance (1 subject), and noncompliance with visits (1 subject).

Note: Treatment is based on initial/re-randomized treatment. Percentages are based on number of initial/re-randomized subjects.

Recruitment

First Subject Enrolled: 18 October 2013
Last Subject Completed Study: 18 March 2015

Conduct of the study

Amendments to the Original Protocol

The original protocol, dated 18 March 2013, was amended once on 03 December 2013.

The following are the most important changes covered by the amendment:

- deleted PASI percent change as a secondary efficacy parameter
- narrowed the equivalence margin used to assess clinical equivalence of PASI percent improvement to ± 15
- added additional efficacy assessments at the week 32 visit
- specified that the primary analysis would be based on randomized treatment assignment
- specified that the primary analysis would occur after all subjects completed week 20

Protocol violations

A total of 35 of 350 subjects (10.0%) had 1 or more major protocol violations from baseline through week 16, and the incidence was similar in each treatment group. The most common protocol violation was mis-stratification at randomization because of incorrect assignment to prior biological treatment category. All other major protocol violations occurred in ≤ 2% of subjects overall.

Baseline data

Table 22-Summary of Demographic and Baseline Characteristics by Initial Treatment (Study 20120263 Full Analysis Set)

Variable	Treatment Group A (ABP 501) (N = 175) n (%)	Treatment Group B (Adalimumab) (N = 175) n (%)	Total (N = 350) n (%)
Sex - n (%)			
Women	63 (36.0)	59 (33.7)	122 (34.9)
Men	112 (64.0)	116 (66.3)	228 (65.1)
Ethnicity - n (%)			
Hispanic or Latino	3 (1.7)	3 (1.7)	6 (1.7)
Not Hispanic or Latino	170 (97.1)	169 (96.6)	339 (96.9)
Not allowed to collect	2 (1.1)	3 (1.7)	5 (1.4)
Race - n (%)			
White	167 (95.4)	157 (89.7)	324 (92.6)
Black or African American	0 (0.0)	2 (1.1)	2 (0.6)
Asian	5 (2.9)	8 (4.6)	13 (3.7)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.6)	1 (0.3)
Mixed Race - White, American Indian, or Alaska Native	0 (0.0)	1 (0.6)	1 (0.3)
Other	1 (0.6)	3 (1.7)	4 (1.1)
Unknown	2 (1.1)	3 (1.7)	5 (1.4)
Age (Years)			
Mean (SD)	45.1 (12.95)	44.0 (13.68)	44.6 (13.31)
Median	46.0	41.0	43.0
Min, Max	18, 74	18, 73	18, 74
Weight (kg)			
n	174	173	347
Mean (SD)	88.85 (23.639)	89.33 (19.390)	89.09 (21.595)
Median	84.45	87.70	86.10
Min, Max	48.0, 200.6	52.9, 166.1	48.0, 200.6
Height (cm)			
n	174	173	347
Mean (SD)	172.39 (9.338)	173.38 (9.906)	172.88 (9.624)
Median	172.85	174.00	173.00
Min, Max	150.5, 199.0	151.0, 200.0	150.5, 200.0
BMI (kg/m^2)			
n	174	173	347
Mean (SD)	29.72 (6.573)	29.66 (5.828)	29.69 (6.204)
Median	28.71	28.53	28.67
Min, Max	18.1, 53.9	19.7, 49.6	18.1, 53.9

Note: Treatment is based on initial randomized treatment. Percentages are based on number of initial randomized subjects.

BSA = body surface area; CSR = clinical study report; PASI = Psoriasis Area and Severity Index; Ps = plaque psoriasis; SD = standard deviation; sPGA = static Physician's Global Assessment.

Table 23-Baseline Psoriasis Characteristics by Initial Treatment Group (Full Analysis Set)

Variable	Treatment Group A (ABP 501) (N = 175) n (%)	Treatment Group B (Adalimumab) (N = 175) n (%)	Total (N = 350) n (%)
Duration of Psoriasis (years)			
n	174	173	347
Mean (SD)	19.85 (11.866)	20.34 (13.482)	20.09 (12.682)
Median	18.50	18.00	18.00
Min, Max	0.7, 54.0	0.7, 59.0	0.7, 59.0
Duration of Psoriasis - n (%)			
< 5 years	13 (7.4)	13 (7.4)	26 (7.4)
≥ 5 years	161 (92.0)	160 (91.4)	321 (91.7)
PASI Score			
n	174	173	347
Mean (SD)	19.68 (8.100)	20.48 (7.880)	20.08 (7.990)
Median	17.10	18.30	17.50
Min, Max	12.0, 61.8	12.0, 52.2	12.0, 61.8
BSA Affected by Psoriasis (%)			
n	174	173	347
Mean (SD)	25.3 (15.02)	28.5 (16.82)	26.9 (16.00)
Median	20.0	23.0	21.0
Min, Max	10, 82	10, 90	10, 90
sPGA			
Clear	0 (0.0)	0 (0.0)	0 (0.0)
Almost Clear	0 (0.0)	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	106 (60.6)	102 (58.3)	208 (59.4)
Severe	61 (34.9)	61 (34.9)	122 (34.9)
Very Severe	7 (4.0)	10 (5.7)	17 (4.9)

BSA = body surface area; PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment

Note: Treatment is based on initial randomized treatment. Percentages are based on number of initial randomized subjects.

The frequency of prior biological use for psoriasis, prior use of systemic or phototherapies, and concomitant topical steroid use was generally similar between treatment groups.

The most commonly used prior medications by preferred name were betamethasone/calcipotriol (14.7%) and clobetasol propionate (10.7%). The proportion of subjects who used betamethasone/calcipotriol before study entry was higher in Treatment Group B than in Treatment Group A (18.5% vs 10.9%, respectively).

Numbers analysed

Table 24-Subject Populations by Initial Treatment (All Initially Randomized Subjects)

Population	ABP 501 (N = 175)	Adalimumab (N = 175)	Total (N = 350)
Subjects Initially Randomized[a][n]	175	175	350
Subjects Treated[ab][n (%)]	174 (99.4)	173 (98.9)	347 (99.1)
Subjects Initially Randomized but Not Treated[ab][n (%)]	1 (0.6)	2 (1.1)	3 (0.9)
Full Analysis Set[abc][n (%)]	175 (100)	175 (100)	350 (100)
Re-randomized Analysis Set[abf][n (%)]	152 (86.9)	156 (89.1)	308 (88.0)
Per Protocol Analysis Set for Week 16[bd][n (%)]	157 (89.7)	153 (87.4)	310 (88.6)
Reasons for Exclusion for PP Analysis Set for Week 16[ab][n (%)]			
Did not complete specified treatment through Week 16	8 (4.6)	10 (5.7)	18 (5.1)
Did not have previous failure to psoriatic systemic therapy	0 (0.0)	1 (0.6)	1 (0.3)
Incorrect treatment received	1 (0.6)	2 (1.1)	3 (0.9)
Mis-stratification at randomization	7 (4.0)	6 (3.4)	13 (3.7)

[a] Based on treatment subject randomized to. [b] % = Percent of all initially randomized subjects.
[c] Full Analysis Set (FAS): All subjects randomized in the study, with treatment assignment based on randomized treatment.
[d] Per Protocol (PP) Analysis Set for Week 16: All randomized subjects who have completed the treatment period through Week 16 and did not experience a protocol deviation/violation that affects their evaluation for primary objective of the analyses at week 16. Subjects are summarized according to their actual treatment received.
[f] Safety Analysis Set: All randomized subjects who received at least 1 dose of treatment. Subjects are summarized according to their actual treatment received.

The full analysis set (350 subjects) and the re-randomized analysis set (308 subjects) for all study weeks, and the per-protocol analysis set for visits through week 16 (310 subjects), were used for the efficacy analysis set.

Outcomes and estimation

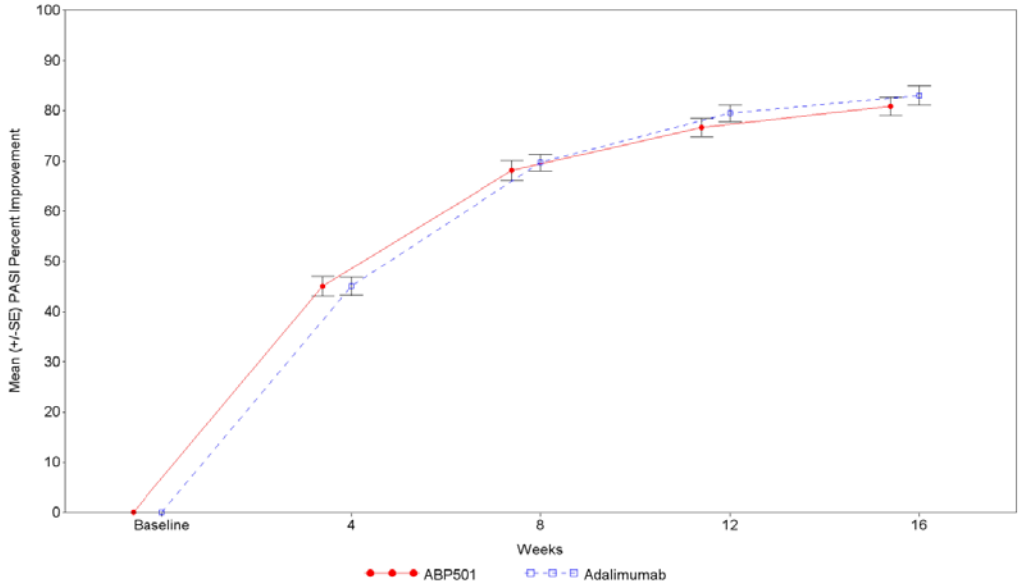
Primary endpoint

Table 25-Summary of PASI Percent Improvement from Baseline to Week 16 (Full Analysis Set, Last Observation Carried Forward)

	Treatment Group A (ABP 501) (N = 175)		Treatment Group B (Adalimumab) (N = 175)	
Timepoint	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Week 16				
n	172	172	173	173
Mean (SD)	3.74 (5.094)	80.91 (24.237)	3.29 (5.795)	83.06 (25.195)
Median	1.80	88.91	2.10	89.39
Min, Max	0.0, 28.8	-71.9, 100.0	0.0, 59.0	-128.7, 100.0
Treatment Difference[a]		-2.18		
p-value		0.4096		
95% CI for Difference[a]		(-7.39, 3.02)		
90% CI for Difference[a]		(-6.55, 2.18)		

CI = confidence interval; PASI = Psoriasis Area and Severity Index
a Estimated using ANCOVA model adjusted for the following factors: prior biologic use for psoriasis, region, and baseline PASI score.

Figure 6-Mean PASI Percent Improvement from Baseline Over Time – Through Week 16 (Full Analysis Set, Last Observation Carried Forward)



PASI = Psoriasis Area and Severity Index
Note: The baseline timepoints were offset to provide clarity and each timepoint was equally spaced for all visits for consistency.

The 95% CI for all sensitivity analyses were within ±10% for all sensitivity analyses, and hence consistent with the primary analysis.

To assess the robustness of the primary PASI percent improvement from baseline results, the primary analysis was repeated using the FAS based on observed cases and the PP analysis set based on observed cases through week 16. When analysed using the FAS as observed and the PP analysis set as observed, the treatment differences in PASI percent improvement from baseline between the ABP 501 and adalimumab treatment groups were -1.46 (2-sided 95% CI: [-6.31, 3.39]) and -2.64 (2-sided 95% CI: [-6.89, 1.60]), respectively.

Secondary endpoints

PASI Percent Improvement from Baseline after Week 16 through Entire Study

Improvement achieved during the first 16 weeks of treatment was maintained over time, equally between groups.

PASI 75 Response

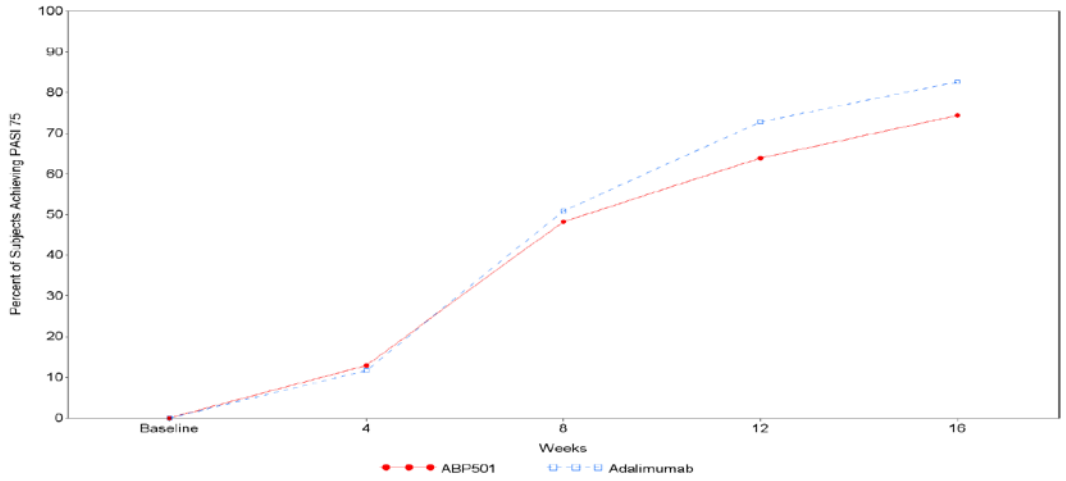
The treatment difference in PASI 75 response for ABP 501 versus adalimumab was -7.729% with the 2-sided 95% CI of (-16.620%, 1.163%).

Table 26- Summary of PASI 75 Response at Week 16 (Study 20120263 Full Analysis Set, LOCF)

Time Point PASI 75 Response	ABP 501 (N = 175) n/N1 (%)	Adalimumab (N = 175) n/N1 (%)
Week 16		
Yes	128/172 (74.4)	143/173 (82.7)
No	44/172 (25.6)	30/173 (17.3)
Treatment difference (%)[a]	-7.729	
95% CI for treatment difference (%)[a]	(-16.620, 1.163)	
90% CI for treatment difference (%)[a]	(-15.191, -0.267)	
Risk ratio[a]	0.929	
95% CI for risk ratio[a]	(0.844, 1.023)	
90% CI for risk ratio[a]	(0.857, 1.008)	

CI = confidence interval; CSR = clinical study report; LOCF = last observation carried forward; n = number of subjects meeting the criteria at the visit; N1 = number of subjects who had an assessment at the visit; PASI 75 = 75% improvem and Severity Index.
a Estimated using a generalized linear model adjusted for the following factors: prior biologic use for psoriasis, region, and baseline PASI score. The risk ratio, treatment difference, and confidence intervals for week 16 were estimated from the generalized linear model with relative Hessian convergence criterion greater than the default limit of 0.0001.

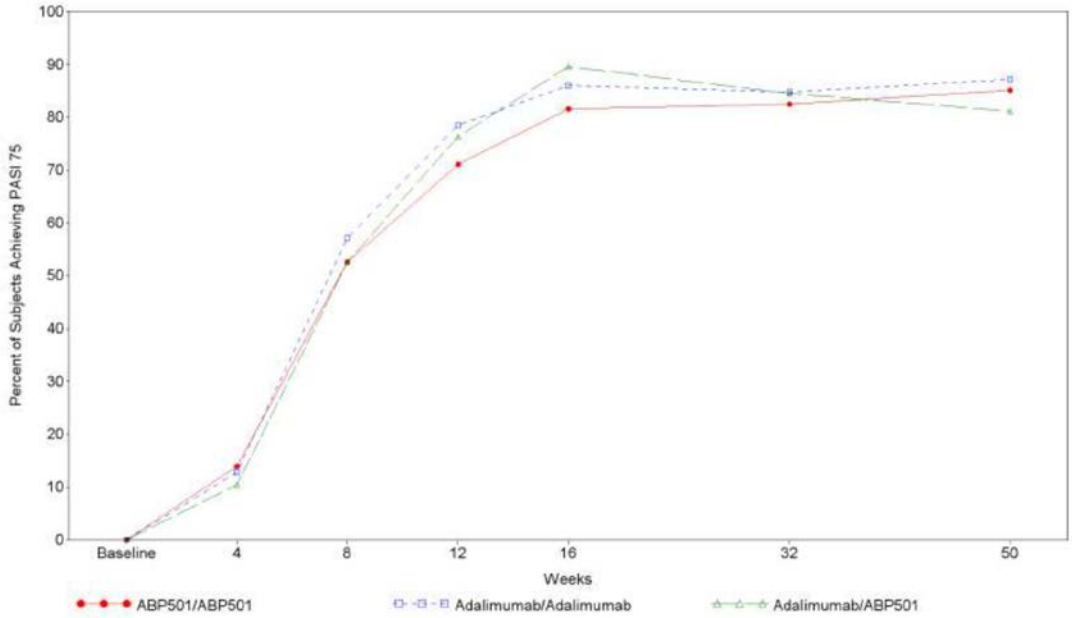
Figure 7-PASI 75 Response Rate over Time - Through Week 16 (Full Analysis Set, LOCF)



PASI 75 Through Entire Study

The PASI 75 responses across the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups, were similar at week 16 (81.6% to 89.6%), week 32 (82.5% to 84.7%), and at week 50 (81.2% to 87.1%). At week 50, the treatment difference between the ABP 501/ABP 501 and adalimumab/adalimumab treatment groups was -4.680% with a 2-sided 95% CI: (-15.263%, 5.904%). The treatment difference at week 50 between the adalimumab/ABP 501 and adalimumab/adalimumab treatment groups was -6.511% with a 2-sided 95% CI of (-19.058%, 6.037%).

Figure 8- PASI 75 Response Rate over Time – Through Entire Study (Study 20120263 Re-randomized Analysis Set, as Observed)

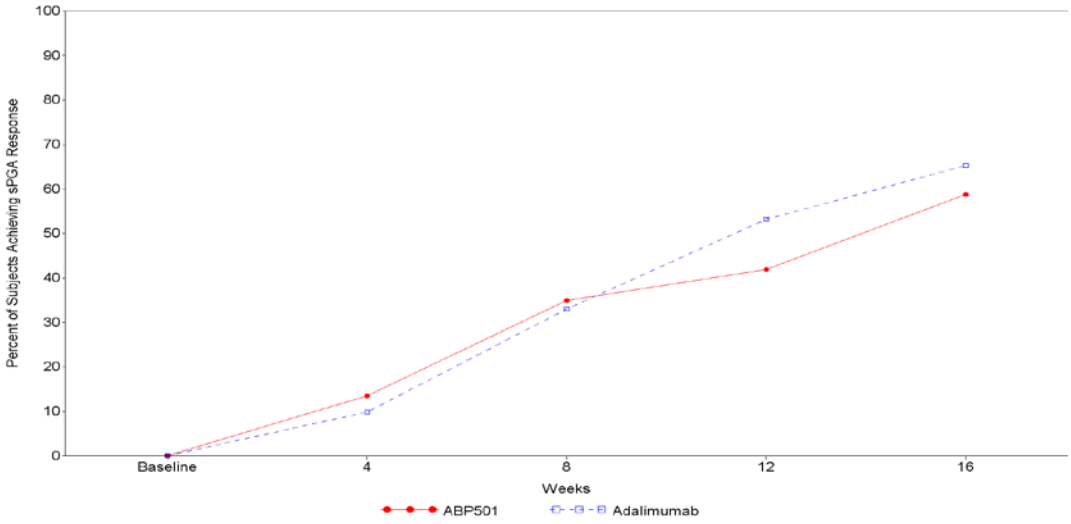


CSR = clinical study report; PASI 75 = ≥ 75% improvement in Psoriasis Area and Severity Index.
Source: Figure 14-4.11.8 in Study 20120263 CSR

Static Physician's Global Assessment

Through Week 16

Figure 9-Static Physician's Global Assessment Rate Over Time - Through Week 16 (Study 2010263 Full Analysis Set, LOCF

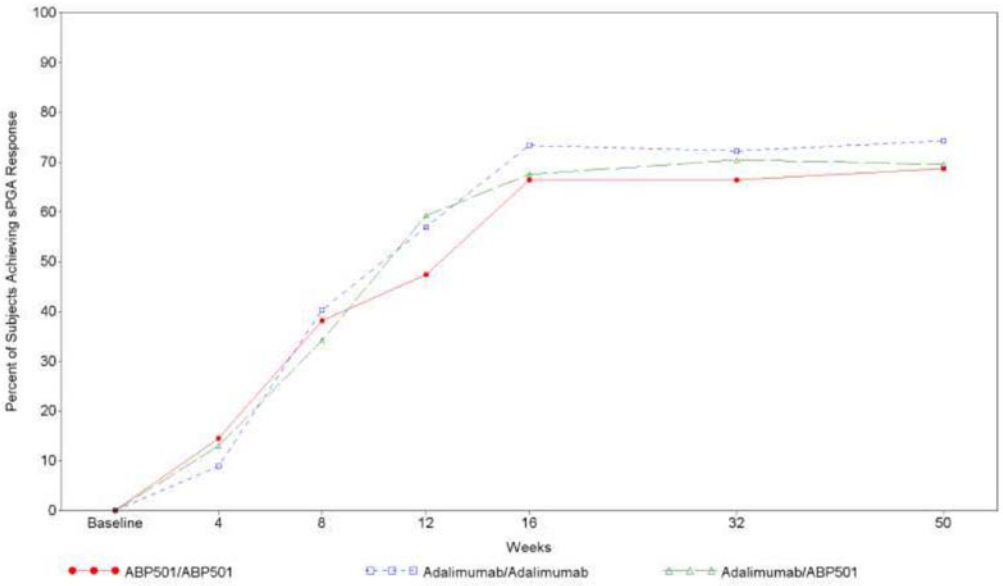


CSR = clinical study report; LOCF = last observation carried forward; sPGA = static Physician's Global Assessment.

In the ABP 501-treated group, 7% less achieved sPGA "clear" or "almost clear"

Through Entire Study

Figure 10-Static Physician's Global Assessment Response (sPGA) Rate over Time – Through Entire Study (Study 20120263 Re-randomized Analysis Set, as Observed)



CSR = clinical study report; sPGA = static Physician's Global Assessment.
Source: Figure 14-4.11.12 in Study 20120263 CSR

Percent Body Surface Area Involvement

At week 16, the mean (SD) percent BSA affected by Ps was 7.4 (11.22) for the ABP 501 treatment group and 6.4 (10.97) for the adalimumab treatment group. Both treatment groups showed a decrease in mean percent BSA (ABP 501, -18.0; adalimumab, -22.1), with a treatment difference of 1.93% with a 2-sided 95% CI of (-0.24%, 4.10%).

Additional Efficacy Analyses

PASI 50 Response

Through Week 16

The PASI 50 response through week 16 (FAS, LOCF) was 159/172 (92.4%) for the ABP 501 treatment group and 163/173 (94.2%)for the adalimumab treatment group. The treatment difference in PASI 50 response between ABP 501 and adalimumab at Week 16 was -2.703% with the 2-sided 95% CI of (-7.786%, 2.380%).

Through Entire Study

At week 50, the treatment difference in PASI 50 response between the ABP 501/ABP 501 and adalimumab/adalimumab treatment groups was 2.783% with a 2-sided 95% CI of (-4.158%, 9.724%).).

PASI 90 Response

Through Week 16

In a post hoc analysis the PASI 90 response through week 16 (FAS, LOCF) was 81/172 (47.1%) for the ABP 501 group and 82/173 (47.4%) for the adalimumab treatment group. The treatment difference in PASI 90 response between ABP 501 and adalimumab at week 16 was 0.3% with the 2-sided 95% CI of (-10.0%, 10.7%) and was not statistically significant (p = 0.9516).

Through Entire Study

At week 50, the treatment difference in PASI 90 response between the ABP 501/ABP 501 and adalimumab/adalimumab treatment groups was -6.3% with a 2-sided 95% CI of (-20.3%, 7.8%) (p=0.3814).

PASI 100 Response

Through Week 16

In a post hoc analysis the PASI 100 response through week 16 (FAS, LOCF) was 29/172 (16.9%) for the ABP 501 group and 34/173 (19.7%) for the adalimumab treatment group. The treatment difference in PASI 100 response between ABP 501 and adalimumab at week 16 was -1.9% with the 2-sided 95% CI of (-10.8%, 7.0%) and was not statistically significant (p = 0.6736).

Through Entire Study

At week 50, the treatment difference in PASI 100 response between the ABP 501/ABP 501 and adalimumab/adalimumab treatment groups was -1.1% with a 2-sided 95% CI of (-15.1%, 13.0%) (p=0.8830).

Immunogenicity

Study 20120263:

- Positive post-baseline binding ADA incidence:

  Through week 16: 55.2% and 63.6% for the ABP 501 and Humira treatment groups, respectively;

  From baseline to the end of study: 68.4%, 74.7%, and 72.7% in the ABP 501/ABP 501, Humira/Humira, and Humira/ABP 501 groups, respectively.

- Positive post-baseline neutralizing ADAs incidence:

  Through week 16: 9.8% ABP 501 and 13.9% Humira, respectively.

  From baseline to the end of study: 13.8%, 20.3% and 24.7% in the ABP 501/ABP 501, Humira/Humira, and Humira/ABP 501 groups, respectively.

The results of the week 16 PASI percent improvement from baseline analyses by neutralizing antidrug antibody status were as follow:

Table 27 - Summary of PASI Percent Improvement from Baseline by Neutralizing Anti-drug Antibodies Status Subgroup (Full Analysis Set, LOCF)

Anti-drug Antibodies Status - On-study Positive at any time through Week 16

	ABP 501 (N = 17)		Adalimumab (N = 24)	
Timepoint	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Week 16				
n	17	17	24	24
Mean (std)	10.02 (7.395)	48.46 (40.465)	8.15 (12.672)	61.91 (48.103)
Median	9.10	57.48	3.50	79.82
Q1, Q3	3.00, 14.70	26.06, 77.62	2.50, 7.00	57.43, 86.84
Min, Max	1.8, 23.1	-71.9, 89.8	0.0, 59.0	-128.7, 100.0
Treatment Difference[a]		-13.30		
95% CI for Difference[a]		(-41.00, 14.40)		
90% CI for Difference[a]		(-36.35, 9.75)		

[a] Estimated using ANCOVA model adjusted for the following factors: prior biologic use for PsO, region and baseline PASI score.

Anti-drug Antibodies Status - On-study Negative throughout Week 16

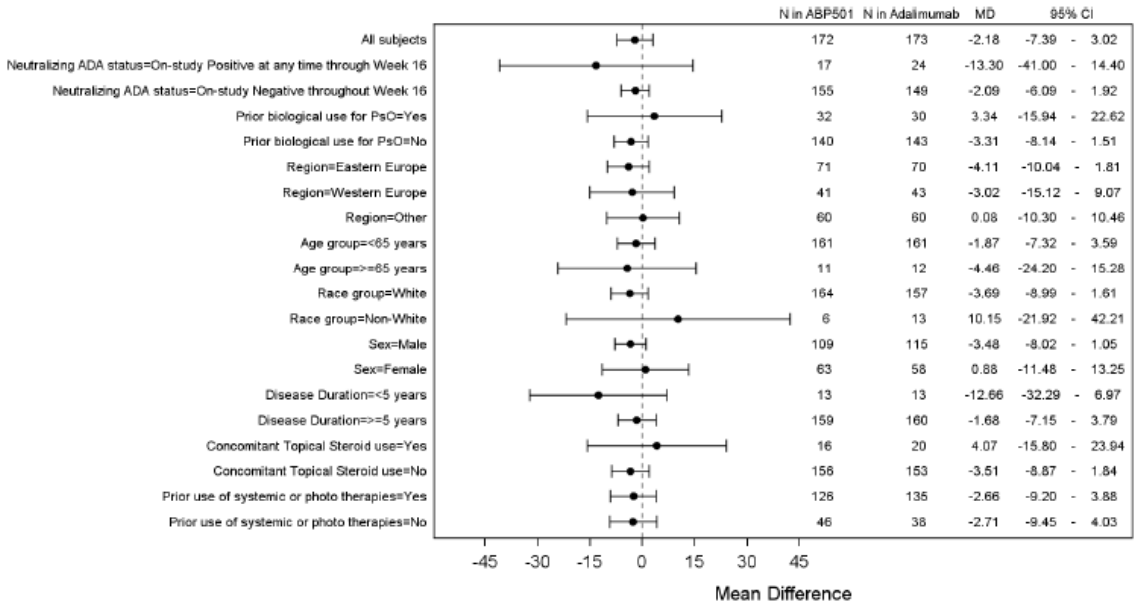
	ABP 501 (N = 157)		Adalimumab (N = 149)	
Timepoint	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Week 16				
n	155	155	149	149
Mean (std)	3.05 (4.279)	84.47 (18.792)	2.51 (3.103)	86.47 (17.145)
Median	1.60	90.91	1.80	90.72
Q1, Q3	0.40, 3.80	79.41, 97.54	0.40, 3.00	81.48, 97.92
Min, Max	0.0, 28.8	9.0, 100.0	0.0, 17.4	-6.1, 100.0
Treatment Difference[a]		-2.09		
95% CI for Difference[a]		(-6.09, 1.92)		
90% CI for Difference[a]		(-5.45, 1.28)		

[a] Estimated using ANCOVA model adjusted for the following factors: prior biologic use for PsO, region and baseline PASI score.

Ancillary analyses

The results of the week 16 PASI percent improvement from baseline were also provided in the following subgroups: prior biologic use for psoriasis, region, age, race, sex, disease duration, concomitant topical steroid use, prior use of systemic or phototherapies, neutralizing antidrug antibody status.

Figure 11-Forest Plot of Mean Difference in PASI Percent Improvement from Baseline at Week 16 (Study 20120263, Full Analysis Set, LOCF)



ADA = antidrug antibody; ANCOVA = analysis of covariance; MD = mean difference; PASI = Psoriasis Area and Severity Index; PsO = plaque psoriasis.
Note: Estimated using ANCOVA model adjusted for prior biologic use for psoriasis, region, and baseline PASI score.

Summary of main studies

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

Table 28-Summary of efficacy for trial 20120262

Title: A randomized, double-blind, active comparator-controlled study in adult subjects with moderate to severe RA who had an inadequate response to MTX.			
Study identifier	20120262-RA		
Design	Randomised, double-blind, active-controlled multicenter study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 4 weeks not applicable	
Hypothesis	Equivalence; equivalence margin for the risk ratio of ACR20 at week 24: [0.738,1/0.738]		
Treatments groups	ABP 501	40 mg SC (Treatment A), every 2 weeks, randomized: n = 264	
	Humira	40 mg SC (Treatment B), every 2 weeks, randomized: n = 262	
Endpoints and definitions	Primary endpoint	ACR20	RR of ACR20 at week 24
	Secondary	ACR20	RR of ACR20 at week 2 and 8
	Secondary	ACR20	RD of ACR20 response at each time point
	Secondary	ACR50	RR and RD of ACR50 response at each time point
	Secondary	ACR70	RR and RD of ACR70 response at each time point
	Secondary	DAS28	Change in DAS28 score from baseline at each time point
Database lock	19 November 2014		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set **week 24**			
Descriptive statistics and estimate variability	Treatment group	ABP 501	Humira	
	Number of subject	264	262	
	ACR20 (Response rate)	74.6%	72.4%	
	ACR50 (Response rate)	49.2%	52%	
	ACR70 (Response rate)	26.0%	22.9%	
	DAS 28 mean	-2.32	-2.32	

Effect estimate per comparison	Primary endpoint ACR20	Comparison groups	ABP 501vs Humira
		Risk Ratio of ACR20	1.039

		95% CI	(0.954, 1.133)
		P-value	N/A
	Secondary endpoint ACR50	Comparison groups	ABP 501vs Humira
		Risk Ratio of ACR50	0.948
		95% CI	(0.819, 1.097).
		P-value	N/A
	Secondary endpoint ACR70	Comparison groups	ABP 501vs Humira
		Risk Ratio of ACR70	1.13
		95%CI	(0.872, 1.464)
		P-value	N/A
	Secondary endpoint DAS28	Comparison groups	ABP 501vs Humira
		Difference in response	-0.01
		95% CI	(-0.22, 0.20)
		P-value	N/A

Analysis description	**Secondary analysis**			
Analysis population and time point description	Full Analysis Set with Non-responder Imputation week 24			
Descriptive statistics and estimate variability	Treatment group	ABP 501	Humira	
	Number of subject	264	262	
	ACR20 (Response rate)	71.2%	72.1%	

Effect estimate per comparison	Primary endpoint ACR20	Comparison groups	ABP 501vs Humira
		Risk Ratio of ACR20	1.00
		9590% CI	(0.915, 1.094)
		P-value	N/A
Notes			

Table 29-Summary of efficacy for trial 20120263

Title: A phase 3, multicenter, randomized, double-blind study that was designed to demonstrate the clinical similarity between ABP 501 and Humira in subjects with moderate to severe plaque psoriasis.		
Study identifier	20120263	
Design	Randomised, double-blind, active-controlled multicenter study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	16 weeks (primary endpoint) 4 weeks 52 weeks (end of study)
Hypothesis	Equivalence; equivalence margin for the difference in PASI percent improvement [-15%, 15%] at week 16	
Treatments groups	ABP501	80 mg SC on week 1/day 1 (initial loading dose) and 40 mg at week 2 and every 2 weeks thereafter, randomized: n = 175

	Humira		80 mg SC on week 1/day 1 (initial loading dose) 40 mg at week 2 and every 2 weeks thereafter, randomized: n = 175
Endpoints and definitions	Primary endpoint	PASI % improvement	PASI percent improvement at week 16
	Secondary	PASI % improvement	PASI percent improvement from baseline at week 32, 50
	Secondary	PASI 75	PASI75 response at week 16, 32 and 50
	Secondary	sPGA	sPGA responses (0/1) at weeks 16, 32, and 50
	Secondary	BSA	BSA involvement at weeks 16, 32, and 50
Database lock	18 March 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set **week 16**		
Descriptive statistics and estimate variability	Treatment group	ABP_501	Humira
	Number of subject	175	175
	PASI % improvement	80.91	83.06
	PASI 75 (Response rate)	74.4%	82.7%
	sPGA (Response rate)	58.7%	65.3%
	BSA	11.22%	10.97%

Effect estimate per comparison	Primary endpoint PASI % improvement	Comparison groups	ABP 501- Humira
		Difference in response	-2.18
		95% CI	(-7.39, 3.02)
		P-value	N/A
	Secondary endpoint PASI 75	Comparison groups	ABP 501- Humira
		Difference in response	-7.729%
		95% CI	(-16.62%, 1.163%)
		P-value	N/A
	Secondary endpoint sPGA	Comparison groups	ABP 501- Humira
		Difference in response	-7.365%
		95% CI	(-17.203%, 2.472%)
		P-value	N/A
	Secondary endpoint BSA	Comparison groups	ABP 501- Humira
		Difference in response	1.93%

		95% CI		(-0.24%, 4.10%)
		P-value		N/A
Analysis description	**Secondary analysis**			
Analysis population and time point description	Full analysis set week 32, 50			
Descriptive statistics and estimate variability	Treatment group	ABP501	Humira/Humira	ABP501/ Humira
	Number of subject	152	79	77
	PASI % improvement week 32/week 50	87.62/87.16	88.16/88.11	86.98/85.82
	PASI 75 week 32/week 50	82.5%/85.1%	84.7%/87.1%	84.5%/81.2%
Effect estimate per comparison	Secondary endpoint PASI % improvement week 32	Comparison groups		ABP 501/ABP 501 vs Humira/Humira; Humira/ABP 501 vs Humira/Humira
		Difference in response		-0.49; -1.05
		95% CI		(-5.60, 4.61); (-6.93, 4.84)
		P-value		N/A
	Secondary endpoint PASI % improvement week 50	Comparison groups		ABP 501/ABP 501 vs Humira/Humira; Humira/ABP 501 vs Humira/Humira
		Difference in response		-1.16; -2.37
		95% CI		(-7.17, 4.86); (-9.26, 4.52)
		P-value		N/A
	Secondary endpoint PASI 75 week 32	Comparison groups		ABP 501/ABP 501 vs Humira/Humira; Humira/ABP 501 vs Humira/Humira
		Difference in response		-2.751; 0.582
		95% CI		(-13.935, 8.433); (-12.899, 14.063)
		P-value		N/A
	Secondary endpoint PASI 75 week 50	Comparison groups		ABP 501/ABP 501 vs Humira/Humira; Humira/ABP 501 vs Humira/Humira
		Adjusted mean difference		-4.680; -6.511
		95% CI		(-15.263, 5.904); (-19.058, 6.037)
		P-value		N/A
Notes				

Analysis performed across trials (pooled analyses and meta-analysis)

Not performed.

Clinical studies in special populations

The purpose of this development program was to evaluate similarity between ABP 501 and the reference product, adalimumab, including an assessment of the effects of any observed differences between the products, if such differences exist. Therefore, in accordance with regulatory guidances, safety studies in special groups (eg, pediatrics and elderly) are not required and are not included in this marketing application. Based on demonstrated analytical, nonclinical, PK, and clinical similarity of ABP 501 to adalimumab, no additional studies in special populations are warranted. This is supported by the CHMP.

Supportive study

PK-study 20110217 was a single-dose study in healthy subjects. It is described and discussed in the Pharmacological section.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy, safety, and immunogenicity similarity of ABP 501 to adalimumab is based on data from Study 20120262 in adult subjects with moderate to severe RA and Study 20120263 in adult subjects with moderate to severe Psoriasis.

The Applicant has sought CHMP advice on the development program, and broadly followed the received recommendations.

<u>20120262 Rheumatoid Arthritis (RA)</u>

The choice of RA population entails concomitant use of MTX, which due to its immune modulatory effect hampers the evaluation of immunogenicity. However, a study in psoriasis was also conducted which gathered further data on immunogenicity.

The inclusion criteria for the RA study are acceptable. The endpoints used are validated and in line with scientific advice, and what has been used in previous RA studies. The primary endpoint was proportion of ACR20 at week 24, and equivalence measured as Risk ratio (RR). The choice of ACR20 as primary endpoint is in accordance with given CHMP Scientific Advice and is endorsed. It is considered acceptable to present the results as RR. Secondary efficacy endpoints used are validated and in line with what has been used in previous RA studies.

The sample size of 500 subjects seems adequate to demonstrate equivalence between the ABP 501 and Humira groups assuming a margin of (0.738, 1/0.738) for the primary efficacy endpoint RR of ACR20. The calculation is based on an expected ACR20 response for both ABP 501 and Humira of 63% at week 24. The choice of the 0.738 margin on a multiplicative scale would correspond to an absolute margin of more than -16% on the additive scale. This could be considered too wide. It is noteworthy that if the same multiplicative margin of 0.738 is considered but assuming a higher expected ACR20 response at week 24 for both arms (i.e. a response of similar magnitude to that obtained in the study:

72%) the resulting absolute margin would be inflated to about -20%. However, in light of the results observed this does not represent an issue that could compromise the reliability of the study.

For DAS-28 CRP, the equivalence margin of ±0.6 was chosen. This has been endorsed in a scientific advice.

Sensitivity analyses used the FAS with non-responder imputation, FAS based on observed cases, and the per protocol (PP) analysis set based on observed cases. Inferential analyses were performed only for the primary endpoint.

Randomisation and blinding methods are acceptable.

All randomized subjects in the US sites assessed their pain at the injection site on a 95-mm horizontal VAS instead of a 100-mm scale due to a printing error. Therefore the results captured on the shorter VAS scale were multiplied by a factor of 100/95. This may not provide correct results in the extremes of the scale, since the choice of point in these regions may be more related to the absolute distance from min/max, than proportion of the whole scale. However, there is no apparent better way to handle this error, which affected both treatment groups equally (68 subjects in the ABP group, 69 in the adalimumab group). It is not considered to significantly impact the evaluation of similarity, which is supported by a sensitivity analysis where the results from the US sites were excluded. CHMP considered that the issue was appropriately handled.

The number of protocol violations was relatively high (10.5%) but equally distributed between groups (9.5% vs 11.5%). The most common major protocol violation was mis-stratification at randomization because of incorrect designation to prior biological use category. This variable was also included as a covariate in the primary analysis and has been used in the analysis model for the primary analysis in order to be consistent with the randomization scheme, and that covariate values collected via the eCRF have been used for subgroup analyses. This is considered acceptable.

Demographic and baseline characteristics were reasonably balanced between the treatment groups.

Study 20120263: Psoriasis

Inclusion and exclusion criteria are acceptable and the study design is generally in line with given scientific advice although the chosen primary endpoint is not the same that was discussed in the Follow up CHMP scientific advice (proportion PASI 75), but percentage improvement in PASI from baseline at Week 16. PASI 75 is used as a secondary endpoint. Primary endpoint was analysed using the full analysis set (FAS) with missing values imputed using LOCF. This is considered acceptable. The equivalence analysis was based on 95% Confidence Intervals which is endorsed. However, the equivalence margin of (-15; 15) in percent improvement in PASI score at week 16 is considered wide. However, the Applicant clarified that the sample size calculation was formally derived using PASI percent improvement (and not the original endpoint PASI75 response) assuming a Standard Deviation (SD) of 31.7. Taking into account the results of the primary endpoint this does not represent an issue that could compromise the reliability of the study.

Randomization and blinding methods are acceptable.

Discontinuation through week 16 was balanced between the treatment groups. The proportion of subjects that completed the IP, as well as the study, was balanced between the 2 groups adalimumab treated patients re-randomized to ABP 501, and re-randomized to stay on adalimumab.

The number of protocol violations was relatively high, but equally distributed between groups.

A total of 59 major protocol violations mainly related to the use of prohibited medication in particular topical steroids, were reported. 36 subjects used any topical corticosteroids through the entire study. However, through week 16 only three (two in the ABP 501 and one in Adalimumab group) out of the 36 subjects were identified as using class I (super potent) and/or class II (potent) topical corticosteroids that were considered prohibited as for protocol. Of these three subjects, only one patient (in the ABP 501 group) was included in the per protocol (PP) analyses. Therefore, this single subject is unlikely to have had any meaningful impact on the analysis of similarity of ABP 501 to adalimumab.

Demographics and baseline psoriasis characteristics were reasonably balanced between the treatment groups. A total of 241 out of 347 IP treated subjects (69.5%) had used topical medications before the study but the medication was stopped before the subject received the first dose of investigational product.

Efficacy data and additional analyses

Study 20120262: Rheumatoid Arthritis (RA)

Primary efficacy endpoint

At week 24, 74.6% of subjects in the ABP 501 group and 72.4% of subjects in the adalimumab group met the ACR20 response criteria. The RR of ACR20 for ABP 501 versus adalimumab was 1.039 with the 2-sided 95% CI (0.938, 1.152). The point estimate is thus close to 1 with a narrow CI and is considered to indicate similarity between ABP 501 and adalimumab.

When calculating the responder rate, LOCF was only used for patients with post-baseline values. A sensitivity analysis including patients with baseline values has been provided. The result does not change the evaluation of clinical equivalence between ABP 501 and the reference product.

The chosen equivalence margin for RR of ACR20 for ABP 501 versus adalimumab at week 24 has not been clinically justified by the applicant. However, the point estimate of the primary endpoint is close to 1 and has narrow CI limits. Given that after 24 weeks of treatment an effect plateau may have been reached, making the end point less sensitive, the totality of data, including response in the respective treatment arms per visit is also highly important.

Secondary efficacy endpoints

At week 2, 35.4% of subjects in the ABP 501 group and 24.5% of subjects in the adalimumab group met the ACR20 response criteria. The RR of ACR20 for ABP 501 versus adalimumab was 1.421 with the 2-sided 95% CI of (1.086, 1.860). ABP 501 thus showed a statistically significant superiority over Humira after 2 weeks treatment. At week 4, the difference between ABP 501 and adalimumab was smaller than week 2, and no longer statistically significant. At weeks 8 and 18 results were very similar between groups, with 95% CI for the risk difference within +/-10%. At week 12, ABP 501 again showed a statistically significant better effect. In summary, at week 2 and week 12, a significant difference in effect between the original product and the biosimilar is seen. However, since there are no statistically significant differences in other variables (ACR50, ACR70 and DAS28-CRP) in early time points, the difference seen at early time points in ACR20 is most likely a chance finding rather than a real difference in onset of action.

In contrast to the ACR20 results, for ACR50, the difference at week 2 was not statistically significant, although the point estimate was well above 1 (RR 1.7). At week 12, there was a difference in favour of adalimumab.

For ACR70 response, no statistically significant differences were seen and the point estimates of RR and RD were low. It should be noted that for ACR70 response, numbers are small, in particular in the beginning of the study.

At week 24, the difference between treatment groups in the mean change from baseline in DAS28-CRP also demonstrated similarity.

At week 24, 30.5% in the ABP 501 treated group and 35.5% in the adalimumab-treated group achieved DAS28-CRP remission. At earlier time points, the opposite was seen, i.e. higher proportions achieving DAS28-CRP remission in the ABP 501-treated group. Numbers are small, however the results also supportive of similarity.

Mean injection site pain rating scores were lower in the ABP 501 group compared with the adalimumab group at each study visit. This difference in scoring rates between groups in favour of ABP 501 is not considered to question biosimilarity, since it is most probably due to differences in excipients.

The incidence of subjects developing binding or neutralizing antibodies was similar between ABP 501 and adalimumab.

Study 20120263: Psoriasis

Primary endpoint

The PASI score decreased substantially through Week 16 in both groups. The mean percent improvement in the ABP 501-treated group was 80.91% vs 83.06% in the adalimumab group. The treatment difference was -2.18% with 95% CI (-7.39, 3.02). This is a narrow CI, well within the predefined interval of ±15%, and also within the more conservative ±10. The results of the primary endpoint are thus considered to be compatible with clinical equivalence.

Secondary endpoints

When looking at the results for the originally discussed primary endpoint, proportion of PASI 75, the point estimate for the treatment difference at week 16 was -7.73% in favour of adalimumab.. Also at earlier visits the same trend was seen. However, clinical equivalence was evaluated only for the primary efficacy endpoint and the margin of ±15 refers only to PASI percent improvement. Moreover, the study was not powered to evaluate equivalence of secondary endpoints against the same pre-defined margin of the primary endpoint.

The difference between groups in favour of adalimumab that was noted for PASI 75 was detected also for sPGA (n.s.). The trend in favour of adalimumab in sPGA was maintained through Week 50. In contrast, the BSA involvement results as well as PASI 50 90 and 100 results are compatible with similarity.

After re-randomisation at week 16 the number of patients per group is subsequently smaller. This results in more uncertain point estimates with wider CIs.

Improvement achieved in PASI during the first 16 weeks of treatment was maintained over time, equally in both groups.

Larger differences between ABP501 and Humira were observed in the PASI percent improvement at week 16, when patients with neutralizing antibodies are considered. However, from baseline to week 50 no important differences were observed in PASI percent improvement between ABP501/ABP501 group and Humira/Humira group in presence of neutralizing-antibodies. Moreover, despite the higher incidence of neutralizing anti-drug antibodies reported in the Humira/ABP 501 group compared to both ABP 501/ABP 501 and Humira/Humira groups it is of reassurance that patients who shifted from

Humira to ABP501 treatment did not show a worsening in efficacy (in terms of PASI percent improvement) compared to patients who remained in Humira treatment. In addition, a clinical review of individual data for neutralizing ADA positive subjects at week 16 was performed along with the titers. Individual data provided, although difficult to analyse, do not seem to suggest a possible correlation between neutralizing ADA titre and efficacy results in either treatment group.

2.5.4. Conclusions on the clinical efficacy

Overall, ABP 501 has in the RA study shown similarity to adalimumab in several analyses. The primary endpoint was met, and similarity at week 24 was indicated with low point estimates and narrow CI intervals both for ACR20 RR and Risk Difference. Also mean change in DAS28-CRP showed high similarity at all visits. ACR20 results per visit showed significant differences which may be interpreted as indicating a faster onset of effect for ABP 501, which could question similarity. However, these results are not seen for DAS28 which is favourable, or for ACR50 or ACR70, and as such it is concluded, that the difference seen at week 2 in ACR20 is likely to be a chance finding rather than a true difference.

Also the psoriasis study met the primary endpoint with a point estimate of difference of 2% with narrow CIs, indicating similarity. The secondary endpoints PASI 75 and sPGA showed point estimates of 7% difference with a wide CI.

Overall, clinical similarity between ABP 501 and adalimumab has been demonstrated.

2.6. Clinical safety

Patient exposure

A total of 1076 subjects were treated with ABP 501 or adalimumab (US or EU) in clinical studies in healthy subjects or patient populations (RA or Ps) (Table 45). Safety findings are reported for 582 subjects administered ABP 501 in the clinical development program. Of note, in Study 20120263, 22.0% (77 of 350) of subjects underwent a single transition in treatment from adalimumab to ABP 501 (adalimumab/ABP 501)

Table 30-Overall Extent of Exposure to Study Treatment (All Clinical Studies)

	Number of Subjects Receiving at Least 1 Dose			
Study Type Study No.	ABP 501 only	Adalimumab only	Adalimumab/ ABP 501	Total
PK Similarity Study in Healthy Subjects				
Study 20110217	67	136[a]	NA	203
Controlled Clinical Studies in Patients				
Study 20120262 (RA)	264	262	NA	526
Study 20120263 (Ps)	174	96	77	347
All Clinical Studies				
Total	505	494	77	1076

EU = European Union; NA = not applicable; PK = pharmacokinetic; Ps = plaque psoriasis; RA = rheumatoid arthritis; US = United States.
a Sixty-nine subjects were exposed to adalimumab (US); 67 subjects were exposed to adalimumab (EU).

In Study 20120262, all 526 subjects randomized received at least 1 dose of IP; therefore, the efficacy population (FAS) is identical to the safety population.

In Study 20120263, 347 of 350 (99.1%) subjects randomized received at least 1 dose of IP; thus, the efficacy population (FAS) and the safety population were similar.

In Study 20110217, all 203 randomized received a single dose of IP; therefore, the PK population described is identical to the safety population.

The proposed dosing regimens for ABP 501 are based on those currently approved for adalimumab for adult and paediatric patients for the indications for which licensure is sought.

In Study 20120262, the overall median exposure duration was 155 days (range 1 to 164 days); the median duration was identical for both the ABP 501 and adalimumab groups. In Study 20120263, from baseline to week 16 (re-randomization), the median exposure duration was 92 days (range 6 to 99 days); the median duration was identical for both the ABP 501 and adalimumab groups. Post week 16, the overall media exposure duration was 225 days (range 1 to 233 days) and was identical for the 3 treatment groups (ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501). Through the entire study (Study 20120263), most subjects received 25 total doses of IP; median exposure was 330 days.

Adverse events

Pharmacokinetic Similarity Study in Healthy Subjects Study 20110217

Table 31-Overall Summary of Treatment-emergent Adverse Events (Study 20110217 Safety Population)

AE Category	ABP 501 (N = 67) n (%)	Adalimumab (US) (N = 69) n (%)	Adalimumab (EU) (N = 67) n (%)	Overall (N = 203) n (%)
Any AE	39 (58.2)	33 (47.8)	46 (68.7)	118 (58.1)
Any grade ≥ 3 AE	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Any treatment-related AE	24 (35.8)	17 (24.6)	28 (41.8)	69 (34.0)
Any AE with outcome of death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any serious AE	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Any AE leading to discontinuation from the study	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)

AE = adverse event; CSR = clinical study report; EU = European Union; US = United States.

Phase 3 Controlled Clinical Studies

Table 32-Overall Summary of Treatment-emergent Adverse Events (Study 20120262 Safety Analysis Set)

AE Category	ABP 501 (N = 264) n (%)	Adalimumab (N = 262) n (%)	Total (N = 526) n (%)
Any AE	132 (50.0)	143 (54.6)	275 (52.3)
Any grade ≥ 3 AE	9 (3.4)	17 (6.5)	26 (4.9)
Any treatment-related AE	50 (18.9)	55 (21.0)	105 (20.0)
Any AE with outcome of death	0 (0.0)	0 (0.0)	0 (0.0)
Any serious AE	10 (3.8)	13 (5.0)	23 (4.4)
AE leading to discontinuation of IP	5 (1.9)	2 (0.8)	7 (1.3)
AE leading to discontinuation from study	7 (2.7)	2 (0.8)	9 (1.7)

Note: Only treatment-emergent adverse events are summarized. For each category, subjects are included only once, even if they experienced multiple events in that category.
AE = adverse event; CSR = clinical study report; IP = investigational product.

Table 33-Overall Summary of Treatment-emergent Adverse Events by Initial Treatment – Through Week 16 (Study 20120263 Safety Analysis Set)

AE Category	ABP 501 (N = 174) n (%)	Adalimumab (N = 173) n (%)	Total (N = 347) n (%)
Any AE	117 (67.2)	110 (63.6)	227 (65.4)
Any grade ≥ 3 AE	8 (4.6)	5 (2.9)	13 (3.7)
Any treatment-related AE	43 (24.7)	43 (24.9)	86 (24.8)
Any AE with outcome of death	0 (0.0)	0 (0.0)	0 (0.0)
Any serious AE	6 (3.4)	5 (2.9)	11 (3.2)
Any AE leading to discontinuation of IP	7 (4.0)	5 (2.9)	12 (3.5)
Any AE leading to discontinuation from study	7 (4.0)	5 (2.9)	12 3.5)

Table 34- Overall Summary of Treatment-emergent Adverse Events by Treatment – Post Week 16 (Study 20120263 Safety Analysis Set)

AE Category	ABP 501/ ABP 501 (N = 152) n (%)	Adalimumab/ Adalimumab (N = 79) n (%)	Adalimumab/ ABP 501 (N = 77) n (%)	Total (N = 308) n (%)
Any AE	108 (71.1)	52 (65.8)	54 (70.1)	214 (69.5)
Any grade ≥ 3 AE	7 (4.6)	2 (2.5)	3 (3.9)	12 (3.9)
Any treatment-related AE	28 (18.4)	18 (22.8)	20 (26.0)	66 (21.4)
Any AE with outcome of death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any serious AE	4 (2.6)	4 (5.1)	4 (5.2)	12 (3.9)
Any AE leading to discontinuation of IP	7 (4.6)	1 (1.3)	3 (3.9)	11 (3.6)
Any AE leading to discontinuation from study	4 (2.6)	1 (1.3)	2 (2.6)	7 (2.3)

Note: Only treatment-emergent adverse events are summarized. For each category, subjects are included only once, even if they experienced multiple events in that category.

AE = adverse event; CSR = clinical study report; IP = investigational product.

Through Entire Study 20120263

Table 35-Overall Summary of Adverse Events by Treatment - Through Entire Study (Safety Analysis Set**)**

	Non Re-randomized		Re-randomized			
Adverse Event Category	**ABP 501 (N = 22) n (%)**	**Adalimumab (N = 17) n (%)**	**ABP 501/ ABP 501 (N = 152) n (%)**	**Adalimumab/ Adalimumab (N = 79) n (%)**	**Adalimumab/ ABP 501 (N = 77) n (%)**	**Total (N = 347) n (%)**
Any Adverse Event	15 (68.2)	11 (64.7)	131 (86.2)	62 (78.5)	66 (85.7)	285 (82.1)
Any Grade >=3 Adverse Event	4 (18.2)	1 (5.9)	10 (6.6)	3 (3.8)	6 (7.8)	24 (6.9)
Any Treatment-Related Adverse Event	8 (36.4)	7 (41.2)	51 (33.6)	23 (29.1)	31 (40.3)	120 (34.6)
Any Grade >=3 Treatment-Related Adverse Event	3 (13.6)	0 (0.0)	4 (2.6)	2 (2.5)	2 (2.6)	11 (3.2)
Any Adverse Event With Outcome of Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any Treatment-Related Adverse Event With Outcome of Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any Serious Adverse Event	3 (13.6)	0 (0.0)	7 (4.6)	4 (5.1)	9 (11.7)	23 (6.6)
Any Treatment-Related Serious Adverse Event	3 (13.6)	0 (0.0)	3 (2.0)	1 (1.3)	1 (1.3)	8 (2.3)
Any Adverse Event Leading to Discontinuation of IP	6 (27.3)	5 (29.4)	8 (5.3)	1 (1.3)	3 (3.9)	23 (6.6)
Any Treatment-Related Adverse Event Leading to Discontinuation of IP	4 (18.2)	3 (17.6)	3 (2.0)	1 (1.3)	2 (2.6)	13 (3.7)
Any Adverse Event Leading to Discontinuation from Study	6 (27.3)	5 (29.4)	5 (3.3)	1 (1.3)	2 (2.6)	19 (5.5)
Any Treatment-Related Adverse Event Leading to Discontinuation from Study	4 (18.2)	3 (17.6)	2 (1.3)	1 (1.3)	1 (1.3)	11 (3.2)

Note: Only treatment-emergent adverse events are summarized.
For each category, subjects are included only once, even if they experienced multiple events in that category.

Common adverse events

Pharmacokinetic Similarity Study in Healthy Subject

In Study 20110217, treatment-emergent adverse events reported for more than 5% of subjects overall, by preferred term were headache, oropharyngeal pain, sinus congestion, nasopharyngitis, and nausea. Of these, headache, oropharyngeal pain and sinus congestion were reported at a higher rate

for the ABP 501-treated group: 28.4% in the ABP 501 group reported headache, as compared to 23.2% in the adalimumab(US) group and 19.4% in the adalimumab(EU) group. If adalimumab is reported together the report rate for headache would be 21.8%.

Phase 3 Controlled Clinical Studies

In Study 20120262, the adverse event by preferred term with the highest subject incidence (≥ 5% overall) was nasopharyngitis (6.8%), and the rates were similar between the 2 groups (6.4% vs 7.3% for the ABP 501 and adalimumab groups respectively). In Study 20120263 through week 16, adverse events by preferred term with the highest subject incidence (≥ 5% overall) were nasopharyngitis (15.0%), headache (8.6%), and upper respiratory tract infection (5.2%), and the rates were similar between the 2 groups.

There were no major differences in frequency of grade 1-4 AEs between treatment groups in either study.

In both studies, treatment-emergent adverse events were most commonly reported in the SOCs of Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Skin and subcutaneous disorders and Gastrointestinal Disorders. Generally, adverse events occurring in ≥ 5% of subjects by SOC were balanced between the 2 treatment groups, except for General Disorders and Administration Site Conditions which occurred at about half the rate in the ABP 501 treatment group in the RA study, and two thirds in the psoriasis study through week 16, as compared to the adalimumab treatment groups.

Events of special interest

The EOIs for the 2 studies in therapeutic indications are based on the known safety risks for adalimumab and include the following: infections, malignancies, hypersensitivity reactions, demyelinating disease, haematological reactions, heart failure, lupus-like syndrome, liver enzyme elevations, and injection site reactions. No events were identified in the EOIs including demyelinating disease or lupus-like syndrome in either study.

Table 36
Study 20120262: **Adverse Events of Interest in Subjects by Treatment Groups (Safety Analysis Set) RA**

	ABP 501 (N = 264)		Adalimumab (N = 262)		Total (N = 526)	
AEs of Interest	Number of Subjects n (%)	Number of Events	Number of Subjects n (%)	Number of Events	Number of Subjects n (%)	Number of Events
Infections	61 (23.1)	92	68 (26.0)	97	129 (24.5)	189
Malignancies	1 (0.4)	2	1 (0.4)	1	2 (0.4)	3
Hypersensitivity	14 (5.3)	18	10 (3.8)	13	24 (4.6)	31
Hematological reactions	5 (1.9)	5	5 (1.9)	5	10 (1.9)	10
Heart Failure	1 (0.4)	1	2 (0.8)	3	3 (0.6)	4
Liver Enzyme Elevations	13 (4.9)	18	10 (3.8)	13	23 (4.4)	31
Injection Site Reactions	6 (2.3)	9	13 (5.0)	39	19 (3.6)	48

Note: Adverse events are coded using MedDRA version 17.1. For each event of interest, subjects are included only once for that event of interest in the number of subjects column. Multiple events were counted separately in the number of events column

Table 37
Study 20120263**: Adverse Events of Interest in Subjects by Treatment Groups – Baseline to Week 16 (Safety Analysis Set) Psoriasis**

	Treatment Group A (ABP 501) (N = 174)		Treatment Group B (Adalimumab) (N = 173)		Total (N = 347)	
Adverse Events of Interest	Number of Subjects n (%)	Number of Events	Number of Subjects n (%)	Number of Events	Number of Subjects n (%)	Number of Events
Infections	59 (33.9)	72	58 (33.5)	76	117 (33.7)	148
Hypersensitivity	8 (4.6)	9	7 (4.0)	8	15 (4.3)	17
Injection Site Reactions	3 (1.7)	4	9 (5.2)	26	12 (3.5)	30
Liver Enzyme Elevations	4 (2.3)	4	2 (1.2)	2	6 (1.7)	6
Hematological reactions	0 (0.0)	0	3 (1.7)	5	3 (0.9)	5
Malignancies	1 (0.6)	1	1 (0.6)	1	2 (0.6)	2

Note: Adverse events are coded using MedDRA version 17.1. Only treatment-emergent adverse events are summarized. For each event of interest, subjects are included only once for that event of interest in the number of subjects column. Multiple events were counted separately in the number of events column.

Hypersensitivity

In the RA study, standard searches identified 31 events of hypersensitivity in 24 of 526 subjects (4.6%); 18 of these events occurred in 14 of 264 subjects (5.3%) in the ABP 501 group and 13 events occurred in 10 of 262 subjects (3.8%) in the adalimumab group.

The most commonly reported (1% or more of subjects overall) hypersensitivity treatment-emergent adverse event was rash (1.9% and 0.4%) for subjects in the ABP 501 and adalimumab treatment groups, respectively.

In the psoriasis study through week 16, standard searches identified 17 events of hypersensitivity in 15 of 347 subjects (4.3%); 9 of these events occurred in 8 of 174 subjects (4.6%) in the ABP 501 group and 8 events occurred in 7 of 173 subjects (4.0%) in the adalimumab group.

In the RA study, 11 ABP 501-treated subjects experienced any kind of rash (PT: rash, rash erythematous, rash pruritic, rash morbilliform, drug eruption) compared to 5 in the adalimumab–treated group (PT rash, rash erythematous, rash pruritic, rash macular). This trend was not observed through Week 16 in the psoriasis study. Through Week 16, 3 cases of Rash (including PTs Rash, Rash pruritic) were reported from the adalimumab group, 0 for ABP 501. Post Week 16 in the psoriasis study 3 subjects experienced rash in the ABP group and 1 in the adalimumab group. Two subjects reported urticaria after switching to ABP 501, however the AE occurred months after the switching in both cases.

Injection site Reactions

There was an imbalance in both studies for injection site reactions, in favour of ABP 501, 2.3% vs 5.0% in the RA study, and 1.7% vs 5.2% in the psoriasis study through Week 16. After the switch in Week 16, no infection site reactions occurred in the adalimumab/ABP 501 group. The Applicant states that “the excipients in ABP 501 and adalimumab drug product are different, which most likely contributed to the difference in pain perception among subjects”.

Incidence of Hypersensitivity and Injection Site Reaction Adverse Events by Antidrug Antibody Status

A post hoc analysis for stratification of hypersensitivity and injection site reactions adverse events by binding ADA and neutralizing ADA status was conducted with summary results for the RA and Ps studies showed in tables below.

Table 38

Incidence of Hypersensitivity and Injection Site Reaction Adverse Events by Antidrug Antibody Status (Study 20120262 in Rheumatoid Arthritis)

Event of Interest	ADA Status[a]	ABP 501 (N = 264) n/N1 (%)	Adalimumab (N = 262) n/N1 (%)
Hypersensitivity reactions	All subjects	14/264 (5.3)	10/262 (3.8)
	Binding ADA +	7/106 (6.6)	2/105 (1.9)
	Binding ADA -	7/158 (4.4)	8/157 (5.1)
	Neutralizing ADA +	2/24 (8.3)	2/29 (6.9)
	Neutralizing ADA -	12/240 (5.0)	8/233 (3.4)
Injection site reactions	All subjects	6/264 (2.3)	13/262 (5.0)
	Binding ADA +	2/106 (1.9)	7/105 (6.7)
	Binding ADA -	4/158 (2.5)	6/157 (3.8)
	Neutralizing ADA +	0/24 (0.0)	1/29 (3.4)
	Neutralizing ADA -	6/240 (2.5)	12/233 (5.2)

ADA = antidrug antibody; n = number of subjects with the specified adverse event; N1 = number of subjects attributed to that ADA status.
Note: Adverse events are coded using MedDRA version 17.1. Only treatment-emergent adverse events are summarized.
[a] ADA + represents a positive result any time during the study. ADA – represents a negative result every time during the study
Source: Table 14-6.1.6.1, Table 14-6.1.6.2, Table 14-6.1.6.3, Table 14-6.1.6.4 in Appendix 1 of this document

Table 39

Incidence of Hypersensitivity and Injection Site Reaction Adverse Events by Antidrug Antibody Status Through Week 16 (Study 20120263 in Plaque Psoriasis)

Event of Interest	ADA Status[a]	ABP 501 (N = 174) n/N1 (%)	Adalimumab (N = 173) n/N1 (%)
Hypersensitivity reactions	All subjects	8/174 (4.6)	7/173 (4.0)
	Binding ADA +	4/97 (4.1)	3/111 (2.7)
	Binding ADA -	4/77 (5.2)	4/62 (6.5)
	Neutralizing ADA +	0/17 (0.0)	0/24 (0.0)
	Neutralizing ADA -	8/157 (5.1)	7/149 (4.7)
Injection site reactions	All subjects	3/174 (1.7)	9/173 (5.2)
	Binding ADA +	2/97 (2.1)	5/111 (4.5)
	Binding ADA -	1/77 (1.3)	4/62 (6.5)
	Neutralizing ADA +	1/17 (5.9)	1/24 (4.2)
	Neutralizing ADA -	2/157 (1.3)	8/149 (5.4)

ADA = antidrug antibody; n = number of subjects with the specified adverse event; N1 = number of subjects attributed to that ADA status.
Note: Adverse events are coded using MedDRA version 17.1. Only treatment-emergent adverse events are summarized.
[a] ADA + represents a positive result any time during the period. ADA – represents a negative result every time during the period
Source: Table 14-6.1.7, Table 14-6.1.8, Table 14-6.1.11, Table 14-6.1.12 in Appendix 1 of this document

Table 40-Incidence of Hypersensitivity and Injection Site Reaction Adverse Events by Antidrug Antibody Status Post Week 16 (Study 20120263 in Plaque Psoriasis)

Event of Interest	ADA Status	ABP 501/ ABP 501 (N = 152) n/N1 (%)	Adalimumab/ Adalimumab (N = 79) n/N1 (%)	Adalimumab/ ABP 501 (N = 77) n/N1 (%)
Hypersensitivity reactions	All subjects	8/152 (5.3)	2/79 (2.5)	3/77 (3.9)
	Binding ADA +	6/98 (6.1)	2/56 (3.6)	0/55 (0.0)
	Binding ADA -	2/54 (3.7)	0/23 (0.0)	3/22 (13.6)
	Neutralizing ADA +	0/21 (0.0)	0/14 (0.0)	0/19 (0.0)
	Neutralizing ADA -	8/131 (6.1)	2/65 (3.1)	3/58 (5.2)
Injection site reactions	All subjects	2/152 (1.3)	3/79 (3.8)	0/77 (0.0)
	Binding ADA +	1/98 (1.0)	2/56 (3.6)	0/55 (0.0)
	Binding ADA -	1/54 (1.9)	1/23 (4.3)	0/22 (0.0)
	Neutralizing ADA +	0/21 (0.0)	1/14 (7.1)	0/19 (0.0)
	Neutralizing ADA -	2/131 (1.5)	2/65 (3.1)	0/58 (0.0)

ADA = antidrug antibody; n = number of subjects with the specified adverse event; N1 = number of subjects attributed to that ADA status.
Note: Adverse events are coded using MedDRA version 17.1. Only treatment-emergent adverse events are summarized.
[a] ADA + represents a positive result any time during the period. ADA – represents a negative result every time during the period
Source: Table 14-6.1.15, Table 14-6.1.16, Table 14-6.1.17, Table 14-6.1.18 in Appendix 1 of this document

Liver Enzyme Elevation Adverse Events

Per protocol, subjects with AST and/or ALT ≥2 times the upper limit of normal at baseline were excluded from the phase 3 studies.

In the RA study liver enzyme elevation events, occurred in 4.9% of subjects in the ABP 501 group and in 3.8% in the adalimumab group.

Also in the psoriasis study, slightly more cases of liver AEs were observed in the ABP 501 group through Week 16. After week 16, i.e. after longer use, there was a more obvious imbalance between the ABP 501/ABP 501 group and the adalimumab group in liver AE (5.9 vs 2.5%).

Serious adverse event and deaths

No subjects died in Study 20110217 or in either phase 3 controlled studies. Serious adverse events were reported infrequently, 4.4% of subjects in Study 20120262 and 6.6% of subjects through the entire study in Study 20120263. No major differences in frequency or pattern of SAEs between treatment arms in the two phase 3 studies have been seen.

Laboratory findings

General haematology and chemistry assessments were conducted in the 3 clinical studies. Overall, there were no clinically meaningful differences in haematology laboratory results between the ABP 501 and adalimumab groups in neither the RA nor the Psoriasis study.

Chemistry Laboratory Results

Serum chemistry (ALT, AST, total bilirubin, alkaline phosphatase, gamma glutamyl transferase [GGT], sodium, potassium, albumin, total protein, non-fasting glucose, urea, and creatinine) laboratory values at baseline and change from baseline were summarized using descriptive statistics at each analysis visit by treatment.

There were slightly more liver AEs in the ABP 501 treated groups. Other chemistry laboratory results did not show major differences between the ABP 501 and adalimumab groups.

Safety in special populations

Subgroup analyses of adverse events by age, race, and sex, and for study 20120262 prior biological use for RA, by SOC showed no notable differences in the subject incidence of adverse events when compared with the overall population and between each treatment group.

Immunological events

Antidrug Antibody Formation

Pharmacokinetic Similarity Study in Healthy Subjects

No pre-existing ADAs were detected in the baseline samples; all ADAs detected during the study developed after dosing with ABP 501 or adalimumab (US or EU)

Table 41-Summary of Antidrug Antibody Results (Study 20110217 Safety Population)

	ABP 501 (N = 67) n (%)	Adalimumab (US) (N = 69) n (%)	Adalimumab (EU) (N = 67) n (%)	Overall (N = 203) n (%)
Day 1	0	0	0	0
Day 16	12 (17.9)	12 (17.4)	23 (34.8)	47 (23.3)
Day 29	21 (31.8)	27 (41.5)	27 (41.5)	75 (38.3)
End of study	29 (43.3)	34 (50.0)	34 (50.7)	97 (48.0)
Overall result	36 (53.7)	38 (55.1)	45 (67.2)	119 (58.6)

CSR = clinical study report; EU = European Union; US = United States.

Table 42-Number and Percentage of Subjects with Neutralizing Antibody Positive Results (Study 20110217)

	Number and Percentage of Subjects with Neutralizing Antibody Positive Results			
Timepoint	ABP 501 (N=67)	Adalimumab (US) (N=69)	Adalimumab (EU) (N=67)	Overall (N=203)
In-Study Only	12 (17.9%)	15 (21.7%)	14 (20.9%)	41 (20.2%)
In-Study and Follow-up	18 (26.9%)	24 (34.8%)	20 (29.9%)	62 (30.5%)

Study 20120262 RA

All 526 subjects who were randomized in this study had at least 1 evaluable antibody test result of ABP 501 or adalimumab and were included in the antibody analysis set.

Table 43-Antidrug Antibodies Summary Results by Treatment (Study 20120262 ADA Analysis Set)

Variable	ABP 501 (N = 264) n (%)	Adalimumab (N = 262) n (%)	Total (N = 526) n (%)
Subjects with an on-study result[a]	264 (100.0)	262 (100.0)	526 (100.0)
Total antibody incidence [n(%)]			
Binding antibody positive anytime	106 (40.2)	105 (40.1)	211 (40.1)
Neutralizing antibody positive anytime	24 (9.1)	29 (11.1)	53 (10.1)
Subjects with a result at baseline [n(%)]	261 (98.9)	261 (99.6)	522 (99.2)
Pre-existing antibody incidence			
Binding antibody positive at or before baseline	5 (1.9)	6 (2.3)	11 (2.1)
Neutralizing antibody positive at or before baseline	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with a post-baseline result	261 (98.9)	260 (99.2)	521 (99.0)
Developing antibody incidence [n(%)]			
Binding antibody positive post-baseline with a negative or no result at baseline	101 (38.3)	100 (38.2)	201 (38.2)
Treatment difference	0.219		
90% CI for treatment difference[b]	(-6.795, 7.234)		
95% CI for treatment difference[b]	(-8.139, 8.578)		
Transient[c]	15 (5.7)	10 (3.8)	25 (4.8)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	24 (9.1)	29 (11.1)	53 (10.1)
Treatment difference	-1.434		
90% CI for treatment difference[b]	(-6.741, 3.874)		
95% CI for treatment difference[b]	(-7.758, 4.890)		
Transient[c]	5 (1.9)	3 (1.1)	8 (1.5)

Note: Baseline is defined as the last non-missing assessment taken prior to the first dose of study IP.

ADA = antidrug antibody; CI = confidence interval; CSR = clinical study report; IP = investigational product; RA = rheumatoid arthritis.

a Subjects considered on-study after signing informed consent form.

b Estimated using a generalized linear model adjusted for the following factors: prior biologic use for RA and region. The treatment difference and its confidence intervals for the neutralizing antibody were estimated from the generalized liner model with relative Hessian convergence criterion greater than the default limit of 0.0001.

c Negative result at the subject's last time point tested within the study period.

Study 20120263 Psoriasis

Through week 16

Table 44-Antidrug Antibodies Summary Results by Treatment – Through Week 16(Study 20120263 ADA Analysis Set)

Variable	ABP 501 (N = 174) n (%)	Adalimumab (N = 173) n (%)	Total (N = 347) n (%)
Subjects with an on-study result[a]	174	173	347
Total antibody incidence [n(%)]			
Binding antibody positive anytime	97 (55.7)	111 (64.2)	208 (59.9)
Neutralizing antibody positive anytime	17 (9.8)	24 (13.9)	41 (11.8)
Subjects with a result at baseline [n(%)]	171	168	339
Pre-existing antibody incidence			
Binding antibody positive at or before baseline	1 (0.6)	2 (1.2)	3 (0.9)
Neutralizing antibody positive at or before Baseline	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with a post-baseline result	172	172	344
Developing antibody incidence [n(%)]			
Binding antibody positive post-baseline with a negative or no result at baseline	96 (55.2)	110 (63.6)	206 (59.4)
Treatment differences	-8.122		
95% CI for treatment difference[b]	(-18.242, 1.998)		
90% CI for treatment difference[b]	(-16.615, 0.371)		
Transient[c]	9 (5.2)	7 (4.0)	16 (4.6)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	17 (9.8)	24 (13.9)	41 (11.8)
Treatment differences	-3.531		
95% CI for treatment difference[b]	(-10.392, 3.331)		
90% CI for treatment difference[b]	(-9.289, 2.228)		
Transient[c]	0 (0.0)	1 (0.6)	1 (0.3)

ADA = antidrug antibody; CI = confidence interval; CSR = clinical study report; Ps = plaque psoriasis.

a Subjects considered on-study after signing informed consent.

b Estimated using a generalized linear model adjusted for the following factors: prior biologic use for Ps and region.

c Negative result at the subject's last time point tested within the study period.

Trough Entire Study

The upper 95% CIs for difference in the incidence of developing binding antibodies for ABP 501/ABP 501 versus adalimumab/adalimumab and for adalimumab/ABP 501 versus adalimumab/adalimumab

were below the pre-specified margin of 21.7% demonstrating no increased risk of immunogenicity with ABP 501 compared with adalimumab.

Table 45-Anti-Drug Antibodies Summary Results by Treatment for ABP 501 or Adalimumab Assay - Through Entire Study (ADA Analysis Set)

	Non Re-randomized		Re-randomized			
Variable	ABP 501 (N = 22) n (%)	Adalimumab (N = 17) n (%)	ABP 501/ ABP 501 (N = 152) n (%)	Adalimumab/ Adalimumab (N = 79) n (%)	Adalimumab/ ABP 501 (N = 77) n (%)	Total (N = 347) n (%)
Subjects with a Post-baseline Result Developing Antibody Incidence [n (%)]	21	17	152	79	77	346
Binding Antibody Positive Post-baseline with a Negative or No Result at Baseline	18 (81.8)	14 (82.4)	104 (68.4)	59 (74.7)	56 (72.7)	251 (72.3)
Treatment Difference	-4.079		-4.064		-0.159	
95% CI for Treatment Difference[b]	(-36.153, 27.995)		(-15.703, 7.574)		(-13.293, 12.974)	
90% CI for Treatment Difference[b]	(-30.996, 22.839)		(-13.831, 5.703)		(-11.181, 10.863)	
Transient[c]	0 (0.0)	0 (0.0)	33 (21.7)	18 (22.8)	9 (11.7)	60 (17.3)
Neutralizing Antibody Positive Post-baseline with a Negative or No Result at Baseline	13 (59.1)	7 (41.2)	21 (13.8)	16 (20.3)	19 (24.7)	76 (21.9)
Treatment Difference	20.604		-5.513		3.787	
95% CI for Treatment Difference[b]	(-11.044, 52.253)		(-16.048, 5.022)		(-9.373, 16.947)	
90% CI for Treatment Difference[b]	(-5.956, 47.165)		(-14.354, 3.329)		(-7.257, 14.831)	
Transient[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.3)	2 (0.6)

Note: Baseline is defined as the last non-missing assessment taken prior to the first dose of study IP.

b Estimated using a generalized linear model adjusted for the following factors: prior biologic use for PsO and region.

c Negative result at the subject's last time point tested within the study period.

Safety related to drug-drug interactions and other interactions

In accordance with the EMA biosimilar guideline (EMEA/CHMP/BMWP/42832/2005), no further specific studies on the potential impact of drug interactions were submitted with ABP 501.

Discontinuation due to adverse events

Phase 3 studies

Table 46-Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Product or study by Treatment – Through Week 16

Study20120262 Safety Analysis Set	ABP 501 (N = 264) n (%)	Adalimumab (N = 262) n (%)	Total (N = 526) n (%)
Leading to Discontinuation of Investigational Product	5 (1.9)	2 (0.8)	7 (1.3)
Leading to Discontinuation from Study	7 (2.7)	2 (0.8)	9 (1.7)
Study20120263 Safety Analysis Set)	ABP 501 (N = 174) n (%)	Adalimumab (N = 173) n (%)	Total (N = 347) n (%)

Leading to Discontinuation of Investigational Product	7 (4.0)	5 (2.9)	12 (3.5)
Leading to Discontinuation from Study	7 (4.0)	5 (2.9)	12 (3.5)

Post Week 16 Study20120263

Study20120263 Safety Analysis Set)	ABP 501 (N = 152) n (%)	Ada/ada (N = 79) n (%)	Ada/ABP 501 (N = 77	Total (N = 308) n (%)
Leading to Discontinuation of Investigational Product	7 (4.6)	1 (1.3)	3 (3.9)	11 (3.6)
Leading to Discontinuation from Study	4 (2.6)	1 (1.3)	2 (2.6)	7 (2.3)

Post marketing experience

No post-marketing data were submitted.

2.6.1. Discussion on clinical safety

A total of 1076 subjects were treated with ABP 501 or adalimumab (US or EU) in clinical studies in healthy subjects or patient populations (RA or Psoriasis). Safety findings are reported for 582 subjects administered ABP 501 in the clinical development program. Of note, in Study 20120263, 22.0% (77 of 350) of subjects underwent a single transition in treatment from adalimumab to ABP 501 (adalimumab/ABP 501). Safety results were reported per study.

In Study 20120262, in subjects with moderate to severe rheumatoid arthritis, in the ABP-treated group, more subjects discontinued investigational product (IP) (6.8% vs 4.6%) and study continuation (8.0% vs 4.2%). The major reasons were AEs and consent withdrawal. There was no trend of specific AEs leading to withdrawal, and no major difference in frequency between groups.

In the RA study, 4.6% more subjects in the adalimumab group experienced any AE.In the psoriasis study, AEs were reported for 3.6% more subjects in the ABP 501 group at Week 16. If pooled, the difference after 16 weeks of treatment was 1.4% in favour of ABP 501. The described differences in AE rates between treatment groups within the Gastrointestinal Disorder SOCs are based on small numbers, and the difference between groups in the psoriasis study was not seen in the RA study and is not considered to question the similarity.

Through the entire psoriasis study, it was noted that there is a slight difference in any AE rates between the group that stayed on adalimumab (78.5%) and the groups that switched to ABP 501 (85.7%) or received it through the whole study (86.2%). The Applicant provided on request recalculated AE tables 26, 27 and 28, where injection site reactions were excluded. When adjusted for

the lower incidence of local reactions for ABP 501, the imbalance in any AEs between groups does not increase, probably because most of the subjects with injection site reactions also experienced other AEs. No particular PT contributing to the imbalance was identified, and there was no trend for more SAEs among the ABP 501-treated subjects.

In the phase I study in healthy subjects, headache, oropharyngeal pain and sinus congestion were reported at a higher rate for the ABP 501-treated group (28.4%), than in the pooled adalimumab group (21.8%). In contrast, no difference in headache rate was seen in the RA study, and in the psoriasis study the difference was in favour of ABP 501. These diverging results make it plausible that they are by chance findings.

No subjects died in Study 20110217 or in either phase 3 controlled studies. Serious adverse events were reported infrequently, 4.4% of subjects in Study 20120262 and 6.6% of subjects through the entire study in Study 20120263.No major differences in frequency or pattern of SAEs between treatment arms in the two phase 3 studies have been seen. Numerically, slightly more events in the ABP 501 group were seen in the psoriasis study, the opposite in the RA study. No difference in SAE rates between subjects who continued on Adalimumab in subjects who switched to ABP 501 was seen during the 32 weeks after the switch.

Post Week 16 in the psoriasis study, there was an imbalance between ABP 501 and adalimumab in the infection SOC, mainly driven by PTs representing viral infections, or infections where virus is the predominant pathogen, (nasopharyngitis, URTI, influenza, Oral herpes, Pharyngitis, Rhinitis, herpes zoster, viral infection, laryngitis, viral pharyngitis). In study 20120263 through 16 weeks, the higher incidence of infections in the ABP 501 group was not seen, and in study 20120262 the difference was smaller. The results are considered to be by chance findings.

In the RA study, 11 ABP 501-treated subjects experienced any kind of rash (PT: rash, rash erythematous, rash pruritic, rash morbilliform, drug eruption) compared to 5 in the adalimumab–treated group (PT rash, rash erythematous, rash pruritic, rash macular). This trend was not observed through Week 16 in the psoriasis study. Through Week 16, 3 cases of Rash (including PTs Rash, Rash pruritic) were reported from the adalimumab group, 0 for ABP 501. Post Week 16 in the psoriasis study 3 subjects experienced rash in the ABP 501 group and 1 in the adalimumab group. Two subjects reported urticaria after switching to ABP 501, however the AE occurred months after the switching in both cases.

There was an imbalance in injection site reactions, in favour of ABP 501. This could be explained by differences in the excipients in ABP 501 and adalimumab drug product, which most likely contributed to the difference in pain perception among subjects.

In both studies, hypersensitivity AEs was higher in ABP501 arms.

Data on hypersensitivity and injection site reactions adverse events stratified by ADA and neutralizing ADA status has been provided for both studies. Overall, although a certain trend is noted between ADA positivity and occurrence of hypersensitivity reactions in ABP501 treated subjects, the limited number of subgroups hampers a sound conclusion.

In the RA study liver enzyme elevation events, occurred in 4.9% of subjects in the ABP 501 group and in 3.8% in the adalimumab group. Also in the psoriasis study, slightly more cases of liver AEs were observed in the ABP 501 group through Week 16 with a more obvious imbalance between the ABP 501/ABP 501 group and the adalimumab group post week 16 in liver AE (5.9 vs 2.5%). However, numbers are small, and the reported events occurred to a large extent in subjects with abnormal baseline values.

Besides the liver AEs discussed above, there were no clinically meaningful differences in laboratory results between the ABP 501 and adalimumab groups in neither the RA nor the Psoriasis study.

The purpose of this biosimilar development program is to evaluate similarity between ABP 501 and the reference product, adalimumab, including an assessment of the effects of any observed differences between the products, if such differences exist. Therefore, in accordance with regulatory guidances, safety studies in special groups (eg, pediatrics and elderly) are not required and are not included in this marketing application.

In the RA study, the incidence of subjects developing binding or neutralizing antibodies was similar between ABP 501 and adalimumab.

When evaluating anti-drug antibodies (ADA), in the RA study, the point estimate for the difference in ADA rate is very low, 0.219% (-8.139%, 8.578%). Through Week 16 in the psoriasis study, the treatment difference was higher, -8.122% (-18.242%, 1.998%). Since it is in favour of the biosimilar candidate, this was considered to be acceptable by CHMP since it is in accordance with "Guideline on similar biological medicinal products containing monoclonal antibodies" (EMA/CHMP/BMWP/403543/2010). In the psoriasis study, subjects did not use MTX concomitantly, and this is probably the explanation for the higher rate of ADAs in this population.

It is noted that the ADA rate was high through the entire psoriasis study, lasting for 52 weeks (68.4%, 74.7% and 72.7% in the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 groups, respectively). However, there were no indications of an increased incidence of ADAs after switching from adalimumab to ABP 501, and no increase in clinical hypersensitivity reactions in the adalimumab/ABP 501 group.

In Study 20110217 immunogenicity between treatments was similar. It is noted that the rates of ADAs and neutralizing antibodies are high, and rising over time after only one injection, but the results do not question similarity.

The treatment difference for the rate of neutralizing ADAs did not raise concerns for similarity.

2.6.2. Conclusions on the clinical safety

The safety profile of ABP 501 and Humira is considered comparable.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Serious infections including diverticulitis and opportunistic infections, eg, invasive fungal infections, parasitic infections, legionellosis, and tuberculosis
	Reactivation of hepatitis B
	Pancreatitis
	Lymphoma
	Hepatosplenic T-cell lymphoma
	Leukemia

	Non-melanoma skin cancer
	Melanoma
	Merkel cell carcinoma
	Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)
	Immune reactions – lupus-like reaction
	Immune reactions – allergic reactions
	Sarcoidosis
	Congestive heart failure
	Myocardial infarction
	Cerebrovascular accident
	Interstitial lung disease
	Pulmonary embolism
	Cutaneous vasculitis
	Stevens-Johnson Syndrome
	Erythema multiforme
	Worsening and new onset of psoriasis
	Hematologic disorders
	Intestinal perforation
	Intestinal stricture in Crohn's disease
	Liver failure and other liver events
	Elevated alanine aminotransferase levels
	Autoimmune hepatitis
	Medication errors and maladministration
Important potential risks	Other malignancies (except lymphoma, hepatosplenic T-cell lymphoma, leukemia, non-melanoma skin cancer, and melanoma)
	Vasculitis (noncutaneous)
	Progressive multifocal leukoencephalopathy
	Reversible posterior leukoencephalopathy syndrome
	Amyotrophic lateral sclerosis
	Colon cancer in ulcerative colitis patients
	Infections in infants exposed to adalimumab in utero
	Off-label use
Missing information	Use in pregnant and lactating women
	Long-term safety information in the treatment of children, aged from 6 years to less than 18 years with Crohn's disease
	Subjects with immune-compromised conditions either due to underlying conditions (ie, diabetes, renal or

	liver failure, human immunodeficiency virus infection, alcohol or illicit drug abuse), or due to medications (postcancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications Remission-withdrawal-retreatment non-radiographic axial spondyloarthritis/axial spondyloarthritis without radiographic evidence of axial spondyloarthritis, and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis, and polyarticular juvenile idiopathic arthritis Long-term safety data in the treatment of adults with hidradenitis suppurativa Long-term safety data in the treatment of adults with uveitis

Pharmacovigilance plan

Study / Activity Type, title and category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status**	**Date for Submission of Interim or Final Reports**
(ABP 501) 20160264: An observational study to evaluate long-term safety of AMGEVITA/Solymbic in patients with rheumatoid arthritis Category 3	Primary objectives: Assess the long-term safety of AMGEVITA/Solymbic by evaluation of adverse events of special interest (identified risks of adalimumab) in RA patients exposed to AMGEVITA/Solymbic. Compare the current estimated rates to historical comparators (only for: serious infections including diverticulitis and opportunistic infections, eg, invasive fungal infections, parasitic infections, legionellosis, and tuberculosis; and immune reactions – allergic reactions). Secondary objective: Evaluate incidence rates of other adverse events of interest (identified risks of adalimumab). • Secondary objective: Evaluate incidence rates of other adverse events of interest (identified risks of adalimumab).	Serious infections including diverticulitis and opportunistic infections, eg, invasive fungal infections, parasitic infections, legionellosis, and tuberculosis Reactivation of hepatitis B Immune reactions – allergic reactions (hypersensitivity) Non-melanoma skin cancer Melanoma Lymphoma Congestive heart failure Myocardial infarction Cerebrovascular accident Interstitial lung disease Cutaneous vasculitis Hematologic disorders Elevated alanine aminotransferase levels Liver failure and other liver events Demyelinating disorders (including multiple sclerosis, Guillain Barré syndrome, and optic neuritis) Use in pregnant and lactating women	Under development	Interim reports: Yearly from study start date Final report: 2027 3Q

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Serious infections including diverticulitis and opportunistic infections, eg, invasive fungal infections, parasitic infections, legionellosis, and tuberculosis	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material
Reactivation of hepatitis B	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material
Pancreatitis	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Lymphoma	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material

Hepatosplenic T-cell lymphoma	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material
Leukemia	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material
Non-melanoma skin cancer	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material
Melanoma	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material
Merkel cell carcinoma	Relevant text is provided in the following	• Patient Alert Card

	sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• HCP Educational Material
Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material
Immune reactions –lupus-like reaction	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Immune reactions – allergic reactions	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	None
Sarcoidosis	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL:	• None

	• Section 4, Possible side effects	
Congestive heart failure	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA • Section 4, Possible side effects	• Patient Alert Card • HCP Educational Material
Myocardial infarction	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Cerebrovascular accident	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Interstitial lung disease	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Pulmonary embolism	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Cutaneous vasculitis	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects.	None

Stevens-Johnson syndrome	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Erythema multiforme	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Worsening and new onset of psoriasis	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Hematologic disorders	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Intestinal perforation	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Intestinal stricture in Crohn's disease	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the AMGEVITA PIL: None	None
Liver failure and other liver events	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL:	None

	• Section 4, Possible side effects	
Elevated alanine aminotransferase levels	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Autoimmune hepatitis	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None
Medication errors and maladministration	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.2, Posology and administration Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 3, How to use AMGEVITA	None
Important Potential Risks		
Other malignancies (except lymphoma, hepatosplenic T-cell lymphoma, leukemia, non-melanoma skin cancer, and melanoma)	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: None	• Patient Alert Card • HCP Educational Material
Vasculitis (noncutaneous)	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 4, Possible side effects	None

Progressive multifocal leukoencephalopathy	None	None
Reversible posterior leukoencephalopathy syndrome	None	None
Amyotrophic lateral sclerosis	None	None
Colon cancer in ulcerative colitis patients	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the AMGEVITA PIL: None	• Patient Alert Card • HCP Educational Material
Infections in infants exposed to adalimumab in utero	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.6, Fertility, pregnancy, and lactation Relevant text is provided in the following sections of the AMGEVITA PIL: None	None
Off-label use	None	None
Missing Information		
Use in pregnant and lactating women	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.6, Fertility, pregnancy, and lactation Relevant text is provided in the following sections of the AMGEVITA PIL: • Section 2, What you need to know before you use AMGEVITA	None
Long-term safety information in the treatment of children, aged from 6 years to less than 18 years with Crohn's disease	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.2, Posology and method of administration Relevant text is provided in the following sections of the AMGEVITA PIL: None	None
Subjects with immune-compromised conditions either due to underlying conditions (ie, diabetes, renal or liver failure, human immunodeficiency virus	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.4, Special warnings and precautions for use	None

infection, alcohol or illicit drug abuse), or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications	Relevant text is provided in the following sections of the AMGEVITA PIL: None	
Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis, and polyarticular juvenile idiopathic arthritis	None	None
Long-term safety data in the treatment of adults with hidradenitis suppurativa	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.2 Posology and method of administration Relevant text is provided in the following sections of the AMGEVITA PIL: None.	None
Long-term safety data in the treatment of adults with uveitis	Relevant text is provided in the following sections of the AMGEVITA SmPC: • Section 4.2, Posology and method of administration Relevant text is provided in the following sections of the AMGEVITA PIL: None.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the

applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, AMGEVITA (adalimumab) is included in the additional monitoring list as new biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

AMGEVITA is being developed as a biosimilar candidate to Humira (adalimumab). The proposed indications for AMGEVITA are those approved for Humira.

3.1.2. Main clinical studies

The efficacy, safety, and immunogenicity similarity of ABP 501 to adalimumab is based on data from Study 20120262 in adult subjects with moderate to severe RA and Study 20120263 in adult subjects with moderate to severe Plaque Psoriasis.

3.2. Favourable effects

ABP 501 has been developed as an adalimumab biosimilar. In the development of a biosimilar product, there is no requirement to demonstrate benefit to the patient per se as this has been shown for the reference product. The purpose of a biosimilar application is therefore to demonstrate similarity to the reference product. This has been assessed from a quality, non-clinical, pharmacokinetic and clinical perspective, and the conclusion is based upon the totality of data.

From a quality and non-clinical perspective, data has been presented that shows that ABP 501 is highly similar to the reference product Humira.

From a pharmacokinetic perspective, pharmacokinetic similarity is considered sufficiently demonstrated between ABP 501 and the reference product.

From a clinical perspective, two phase 3 studies have been performed, in RA and psoriasis. The point estimate of the primary endpoint of the RA study (RR of ACR20 at week 24 between ABP 501 and Humira) was 1.039 with the 2-sided 95% CI of RR (0.938, 1.152) and in the psoriasis study the point estimate of the primary endpoint (difference in PASI percent improvement at week 16 between ABP 501 vs Humira) was-2.18 with 95% CI (-7.39, 3.02). Thus, the Primary endpoints were met in both studies, with small point estimates for the difference between the reference product and ABP 501, with 95% CI within narrow limits. Equivalence has been shown.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties or limitations that have an impact on the benefit-risk balance.

3.4. Unfavourable effects

The unfavourable effects of ABP 501 are similar to those of Humira, and this application aimed to show that the safety profiles of Humira and ABP 501 are similar. Overall, the safety profile of ABP 501 is considered to be highly similar to that of Humira. No major safety concerns were detected.

3.5. Uncertainties and limitations about unfavourable effects

Through the entire psoriasis study, it is noted that there is a slight difference in any AE rates between the group that stayed on adalimumab (78.5%) and the groups that switched to ABP 501 (85.7%) or received it through the whole study (86.2%). The difference does not seem to be driven by particular PTs, and recalculating AE tables with local AEs excluded did not change the outcome.

After week 16, i.e. after longer use, there is an imbalance between the ABP 501/ABP 501 group and the adalimumab group in liver AE (5.9 vs 2.5%). However, numbers are small, several of the ABP 501 treated subjects with abnormal liver enzymes had elevated values also at baseline, and it is considered unlikely that this imbalance reflects non similarity.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The Applicant provided a thorough comparative exercise in terms of quality, efficacy and safety parameters in line with EU guidance to demonstrate biosimilarity between ABP 501 and Humira.

3.6.2. Balance of benefits and risks

Since similarity has been convincingly shown, the benefit-risk balance of ABP 501 is regarded as equal to the BR balance of Humira in its authorized indications. Thus, the BR balance of ABP 501 is considered as positive.

With the totality of evidence, the CHMP considered that it was justifiable to extrapolate the equivalent clinical efficacy and the comparable safety profile from the ABP 501 studies in RA patients to all of the indications where Humira has been approved

3.7. Conclusions

The overall Benefit/Risk balance of AMGEVITA is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of AMGEVITA is favourable in the following indication:

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 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 disease-modifying anti-rheumatic drugs (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 disease-modifying anti-rheumatic drug 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 adult patients with an inadequate response to conventional systemic HS therapy.

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, a corticosteroid, and 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.

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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 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

Prior to launch of AMGEVITA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where AMGEVITA is marketed, all healthcare professionals who are expected to prescribe AMGEVITA have are provided with the following educational package:

- Physician educational material
- Patient information

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient alert card

The Guide for healthcare professionals shall contain the following key elements:

- Relevant information on the safety concerns of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies to be addressed by the additional risk minimisation measures (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable).

The patient alert card shall contain the following key messages:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using AMGEVITA.
- That AMGEVITA treatment may increase the potential risks of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies.
- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the prescriber

The patient information pack should contain:

- Patient information leaflet

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

Not applicable.