Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Adalimumab

Proprietary Product Name: Amgevita

Sponsor: Amgen Australia Pty Ltd

First round report: 9 September 2016
Second round report: 23 December 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

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List of common abbreviations

Abbreviation	Meaning
Ab	Antibody
ABN	Australian Biological Name
ABP 501	Amgevita (adalimumab)
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement criteria
ADA	Anti-drug antibody
AE	Adverse event (not necessarily treatment-related)
Anti-CCP	Anti-cyclic citrullinated peptide
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate aminotransferase
BCC	Basal cell carcinoma
BMI	Body-mass index
BSA	Body surface area
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CPU	Clinical pharmacology unit
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAS28-CRP	Disease Activity Score 28-CRP
DMARD	Disease-modifying anti-rheumatic drug
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate

Abbreviation	Meaning
EU	European Union
EULAR	European League Against Rheumatism
IP	Investigational product
IV	Intravenous
JIA	Juvenile idiopathic arthritis
Hb	Haemoglobin
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
INN	International Non-proprietary Name
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LPLV	Last patient, last visit
mbTNF-α	transmembrane TNF alpha
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PBRER	Periodic benefit-risk evaluation report
PSUR	Periodic safety update report
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAP	Statistical analysis plan

Abbreviation	Meaning
SC	Subcutaneous(ly)
SCC	Squamous cell carcinoma
SD	Standard deviation
sPGA	static Physician's Global Assessment
sTNF-α	soluble tumour necrosis factor alpha
TB	Tuberculosis
TEAE	Treatment emergent adverse events
TNF	Tumour necrosis factor
ULN	Upper limit of normal
US	United States
UVB	Ultraviolet B

1. Submission details

1.1. Identifying information

Submission number	PM-2016-00845-1-1
Sponsor	Amgen Australia Pty Ltd
Trade name	Amgevita
Active substance	Adalimumab

1.2. Submission type

This is a new application to register Amgevita (company code ABP 501; INN adalimumab) as a medicinal product biosimilar to Humira.

1.2.1. Reference product sourcing

The sponsor supports their application with bioequivalence studies that compare their product, Amgevita, to the reference product, Humira. However, the reference product was sourced in the EU and US. The sponsor has provided justification for this (under 'Rationale for using EU and/or US-sourced Humira as Australian Reference Standard').

1.2.2. Clarification on naming conventions

Throughout the dossier, the sponsor also refers to Amgevita as ABP 501. Consequently, for the purposes of this report, ABP 501 and Amgevita can be and are used interchangeably. The reference product Humira (where sourced from the US) is also referred to as adalimumab (US). The reference product Humira (where sourced from the EU) is also referred to as adalimumab (EU). Under the TGA's current interim naming policy, the sponsor is permitted to refer to Amgevita as adalimumab (the International Nonproprietary Name (INN)/Australian Biological Name (ABN) without the beta extension); however, the sponsor has not done so in their documentation, and for the purposes of this report Amgevita will not be referred to as adalimumab to avoid confusion. An overview of interchangeable names is given in Table 1.

Table 1: Overview of interchangeable names for adalimumab products (for the purposes of this report)

Interchangeable names
Amgevita, **ABP 501**, **adalimumab beta***
Humira (sourced from US), **adalimumab (US)**
Humira (sourced from EU), **adalimumab (EU)**
Humira (unspecified source), **adalimumab**

*adalimumab beta can be used for interim use pending approval as an INN and ABN

1.3. Drug class and therapeutic indication

Adalimumab is a recombinant human immunoglobulin G1 anti-TNFα monoclonal antibody. It binds to human tumour necrosis factor alpha (TNFα) through tumour necrosis factor receptor superfamily (TNFRSF) 1A (p55) and 1B (p75).

Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. Both Amgevita and Humira were manufactured with the use of a Chinese hamster ovary (CHO) cell line. The amino acid sequence of Amgevita is identical to that of Humira.

The sponsor states that the proposed indications for Amgevita are aligned with those currently approved for Humira in Australia, namely:

- Rheumatoid Arthritis;
- Polyarticular Juvenile Idiopathic Arthritis;
- Psoriatic Arthritis;
- Ankylosing Spondylitis;
- Crohn's Disease in Adults and Children (≥6 years);
- Ulcerative colitis;
- Psoriasis.

The proposed indications for Amgevita as outlined in the proposed product information (PI) document, are as follows:

> *<u>Rheumatoid Arthritis</u>*
>
> *Amgevita is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.*
>
> *Amgevita can be used alone or in combination with methotrexate.*
>
> *<u>Polyarticular Juvenile Idiopathic Arthritis</u>*
>
> *Amgevita in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older 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.*
>
> *<u>Psoriatic Arthritis</u>*
>
> *Amgevita is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.*
>
> *<u>Ankylosing Spondylitis</u>*
>
> *Amgevita is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.*
>
> *<u>Crohn's Disease in Adults and Children (≥6 years)</u>*
>
> *Amgevita is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients;*

- *who have had an inadequate response to conventional therapies or,*
- *who have lost response to or are intolerant of infliximab.*

Ulcerative colitis

Amgevita is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time. (see CLINICAL TRIALS).

Psoriasis

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

Comment: It is noted the proposed indications for Amgevita do not include hidradenitis suppurativa. Hidradenitis suppurativa was added as an indication for the reference product Humira (approved on 6 April 2016).

1.4. Dosage forms and strengths

Amgevita will be supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration, supplied as either a 50 mg/mL pre-filled syringe or pre-filled pen (referred to as an autoinjector (AI) in the application). Amgevita will not have a 10 mg strength or a single-use vial as dosage form.

Table 2: Comparison of dosage forms and strengths for Humira and Amgevita

	Humira **Reference product**	**Amgevita** **Biosimilar medicine to Humira**
Dosage forms	single-use pre-filled syringe (10 mg*; 20 mg; 40 mg) single-use pre-filled pen (40 mg only) single-use vial* (40 mg only)	single-use pre-filled syringe (20 mg; 40 mg) single-use pre-filled pen (40 mg only)
Strengths	10 mg* 20 mg 40 mg	20 mg 40 mg

*not available for Amgevita.

1.5. Dosage and administration

The submission proposes registration of the same dosage and administration as the reference product.

Table 3: Recommended dosages for the proposed indications of Amgevita

Indication	Stage	Weight (paediatric indications only)	Dose
Rheumatoid Arthritis	N/A	N/A	40 mg fortnightly (weekly if not on concomitant methotrexate)
Polyarticular Juvenile Idiopathic Arthritis	N/A	10 kg to < 15 kg	10 mg fortnightly*
		15 kg to < 30 kg	20 mg fortnightly
		≥ 30 kg	40 mg fortnightly
Psoriatic Arthritis	N/A	N/A	40 mg fortnightly
Ankylosing Spondylitis	N/A	N/A	40 mg fortnightly
Crohn's Disease	Induction	N/A	160 mg (initial (first) dose) 80 mg (second dose at Day 14)
	Maintenance	N/A	40 mg fortnightly (from Day 28)
Paediatric Crohn's Disease	Induction	< 40 kg	80 mg (initial (first) dose) 40 mg (second dose at Day 14)
		≥ 40 kg	160 mg (initial (first) dose) 80 mg (second dose at Day 14)
	Maintenance	< 40 kg	Moderate CD: 10 mg fortnightly (from Day 28)* Severe CD: 20 mg fortnightly (from Day 28) Treatment may be changed to weekly during flares
		≥ 40 kg	Moderate CD: 20 mg fortnightly (from Day 28) Severe CD: 40 mg fortnightly (from Day 28) Treatment may be changed to weekly during flares
Ulcerative colitis	Induction	N/A	160 mg (initial (first) dose) 80 mg (second dose at Day 14)
	Maintenance	N/A	40 mg fortnightly (from Day 28)

Indication	Stage	Weight (paediatric indications only)	Dose
Psoriasis	Induction	N/A	80 mg (initial (first) dose)
	Maintenance	N/A	40 mg fortnightly (from Day 7)

*no suitable Amgevita presentation available

2. Background

2.1. Information on the condition being treated

2.1.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune multi-system disease, but mainly affects the small joints, symmetrically on both sides. Its main feature is persistent synovitis, leading to irreversible damage to soft tissues and bones in later stages.

2.1.2. Crohn's disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal system of unknown aetiology and characterised by transmural inflammation. It is part of the inflammatory bowel disease (IBD) spectrum. Any part of the GI system may be involved, but the terminal ileum and proximal colon are mostly affected.

2.1.3. Ulcerative colitis

Ulcerative colitis is a relapsing and remitting colitis of unknown aetiology affecting the colonic mucosa. It is part of the inflammatory bowel disease (IBD) spectrum. In approximately half of the cases, only the rectum is affected, but the disease may extend to the colon, or may affect the whole colon.

2.1.4. Ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory spondyloarthritis of unknown aetiology, but with genetic predisposition. It mainly affects the axial skeleton including the sacroiliac region. Its main clinical features are back pain and progressive stiffness of the spine.

2.1.5. Psoriasis and psoriatic arthritis

Psoriasis is a chronic inflammatory skin disorder mainly characterised by erythematous papules and plaques with a silvery scale (plaque psoriasis). However, the disease may also manifest itself as guttate psoriasis, pustular psoriasis, inverse psoriasis, erythrodermic psoriasis, or nail psoriasis. In some individuals, the inflammatory changes extend into joints, leading to psoriatic arthritis.

2.2. Current treatment options

2.2.1. Rheumatoid arthritis

Pharmacological treatment options include:

- Anti-inflammatory medications, for example, nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids

- Non-biological disease-modifying antirheumatic drugs (DMARDs)(for example, methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide)
- Biological DMARDs:
  - Tumour necrosis factor (TNF)-alpha inhibitors (for example, infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol)
  - Interleukin-1 (IL-1) receptor antagonists (for example, anakinra)
  - Interleukin-6 (IL-6) receptor antagonists (for example, tocilizumab)
  - T-cell co-stimulation modulators (for example, abatacept)
  - Anti-CD20 monoclonal antibodies (for example, rituximab)
  - Janus kinase inhibitors (for example, tofacitinib)

2.2.2. Crohn's disease and ulcerative colitis

Pharmacological treatment options include:

- Glucocorticoids (for example, prednisone, budesonide)
- 5-aminosalicylic acid (5-ASA) drugs (for example, mesalamine) or sulfa drugs (for example, sulfasalazine)
- Antimicrobials
- Antidiarrhoeals (for example, loperamide)
- Non-biological immunomodulators (for example, azathioprine, 6-mercaptopurine)
- Biological immunomodulators (for example, infliximab, adalimumab, certolizumab pegol)

2.2.3. Ankylosing spondylitis

Pharmacological treatment options include:

- Anti-inflammatory medications, for example, nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, and glucocorticoids
- Non-biological disease-modifying antirheumatic drugs (DMARDs), often only in conjunction with biological DMARDs
- Biological DMARDs:
  - Tumour necrosis factor (TNF)-alpha inhibitors (for example, infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol)

2.2.4. Psoriasis and psoriatic arthritis

Treatment options include:

- Topical corticosteroids and emollients
- Vitamin D analogues (for example, calcipotriene, calcitriol)
- Topical/systemic retinoids (for example, tazarotene)
- Topical tacrolimus or pimecrolimus
- UVB phototherapy
- Non-biological agents (for example, methotrexate, cyclosporine, apremilast)
- Biological immunomodulators (for example, infliximab, adalimumab, etanercept, ustekinumab secukinumab, ixekizumab)

2.3. Clinical rationale

ABP 501 (Amgevita) has been developed by the sponsor as a similar biological product to the reference product Humira. It can serve as an alternative to the reference product, if found to be biosimilar.

2.4. Formulation

2.4.1. Formulation development

In the Clinical Overview, the sponsor states that the goal of the ABP 501 formulation development plan was: *'to preserve elements of the Humira formulation that may affect purity, safety, potency, and bioavailability'* and '*to maximize ABP 501 stability over shelf life and preserve critical quality attributes under conditions of transportation, light exposure, and patient handling.*'

2.5. Guidance

The following guidelines have been considered in relation to this submission:

General guidelines

CPMP/ICH/135/95 with TGA comments	Note for guidance on good clinical practice (CPMP/ICH/135/95 - Annotated with TGA comments)

Guidelines regarding similar biological medicinal products

Regulation of biosimilar medicines	TGA guidance on regulation of biosimilar medicines, Version 2.0, December 2015
CHMP/437/04 Rev. 1	Guideline on similar biological medicinal products
EMEA/CHMP/BMWP/42832/2005 Rev 1	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
EMA/CHMP/BWP/247713/2012	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)
EMA/CHMP/BMWP/403543/2010	Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues
CPMP/EWP/QWP/1401/98 Rev 1/ Corr **	Guideline on the investigation of bioequivalence

General guidelines regarding biological medicinal products/therapeutic proteins

EMEA/CHMP/BMWP/101695/2006	Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process: non-clinical and clinical issues
EMEA/CHMP/BMWP/14327/2006	Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins
CHMP/EWP/14327/2004	Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins

Guidelines regarding products containing monoclonal antibodies

EMA/CHMP/BMWP/86289/2010	Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use
CPMP/ICH/5721/03	ICH Topic Q 5 E: Comparability of biotechnological/ biological products Note for Guidance on biotechnological/biological products subject to changes in their manufacturing process

Indication-specific guidelines

CHMP/EWP/2454/02 corr	Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis
CPMP/EWP/556/95 rev 1/Final	Points to consider on clinical investigation of medicinal products other than NSAIDS for treatment of rheumatoid arthritis

Guidelines regarding products for long-term use

Rules 1998 (3C) - 3CC6a (pp. 127–132)	Clinical Investigation of Medicinal Products for Long-Term Use

2.6. Evaluator's commentary on the background information

2.6.1. Lack of 10 mg presentation

There are paediatric subgroups within the proposed indications for which there is no appropriate dosage form of Amgevita:

- For the Crohn's disease indication, for paediatric patients with moderate CD, use will be restricted to patients 40 kg and over, as there is no 10 mg presentation. Paediatric patients with severe CD require 20 mg maintenance doses fortnightly and can be accommodated with Amgevita.
- For the polyarticular juvenile idiopathic arthritis the use will be restricted to patients 15 kg and over, as there is no 10 mg presentation.

This is not currently reflected in the indication wording, but relevant statements are present in the proposed PI document.

2.6.2. Alignment with indications of the reference product

The sponsor states that the indications sought are fully aligned with those registered for Humira in Australia. However, hidradenitis suppurativa, currently approved for the reference product Humira, as one of the indications, is not listed. The sponsor should be invited to align the indications of Amgevita with the indications of the reference product.

2.6.3. Extrapolation of indications

The sponsor has conducted equivalence trials in rheumatoid arthritis and psoriasis patients only. The sponsor has proposed the extrapolation indications and provided a justification for this.

2.6.4. Reference product sourcing

The Humira reference products used in the three bioequivalence studies were sourced either in the EU or in the US. A full justification demonstrating that Humira available in Australia is

comparable to Humira available in the EU and US is provided by the sponsor. The justifications will be evaluated in this report.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The dossier does not contain a full development program. The sponsor supports their biosimilar application with three bioequivalence studies that compare their product, Amgevita, to the reference product, Humira:

- one pharmacokinetic similarity study (in healthy subjects) (Study 20110217); and
- two efficacy and safety studies (one study with in patients with RA (Study 20120262), one study in patients with psoriasis (Study 20120263)).

Clinical study reports for:

- Study 20110217: a Phase I, 3 arm parallel group, randomised, single blind, single dose PK similarity study that compared ABP 501 to adalimumab (US) and adalimumab (EU) in 203 healthy men and women.
- Study 20120262: a Phase III, double-blind, randomised, active comparator-controlled study in 526 subjects with moderate to severe rheumatoid arthritis with concomitant methotrexate and oral corticosteroid use evaluating the efficacy and safety of ABP 501 compared with adalimumab (US).
- Study 20120263: a Phase III, double blind, randomised, active comparator-controlled study in 350 subjects with moderate to severe psoriasis with no concomitant medications allowed for the treatment of psoriasis evaluating the efficacy and safety of ABP 501 compared with adalimumab (EU).

3.2. Paediatric data

No paediatric data was submitted. Furthermore, there is no agreed Paediatric Investigation Plan (PIP), as this is not required for biosimilar applications in the EU. At the time of this evaluation, the sponsor was awaiting a waiver from the FDA for not conducting a paediatric assessment.[1]

3.3. Good clinical practice

All studies contained a statement claiming compliance with Good Clinical Practice guidelines.

3.4. Evaluator's commentary on the clinical dossier

The presentation of the dossier is acceptable.

[1] The sponsor has now received a waiver from the FDA.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Studies 20110217, 20120262, and 20120263 provided PK data (Table 4).

Study 20110217 was a dedicated PK study that compared Amgevita to Humira in healthy subjects.

Studies 20120262 and 20120263 were equivalence studies that compared Amgevita to Humira with regard to efficacy in rheumatoid arthritis and psoriasis respectively. The PK component was limited to a comparison of steady state trough concentrations.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	20110217	To demonstrate bioequivalence (as assessed principally by area under the serum concentration-time curve (AUC) from time 0 extrapolated to infinity (AUC_{inf}) and the maximum observed serum concentration (C_{max})) of ABP 501 following a 40 mg subcutaneous (SC) injection relative to that from a 40 mg SC injection of adalimumab (US) (Humira) and adalimumab (EU) (Humira)
	Bioequivalence† - Single dose		
PK in special populations	Target population § - Multi-dose	20120262	To demonstrate pharmacokinetic similarity of ABP 501 to Humira by comparing steady state trough concentrations in patients with rheumatoid arthritis
	Target population § - Multi-dose	20120263	To demonstrate pharmacokinetic similarity of ABP 501 to Humira by comparing steady state trough concentrations in patients with psoriasis

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

The sponsor is planning a further PK study:

- Study 20120176 (at the request of the regulatory authority of Japan): a randomised, single-blind, single-dose, 2-arm, parallel-group study to determine the PK bioequivalence of ABP 501 and adalimumab in 179 healthy adult Japanese subjects. No results for this study were submitted with the current application.

4.1.1. Study 20110217: A randomised, single blind, single dose, 3 arm, parallel group study to determine the pharmacokinetic equivalence of ABP 501 and adalimumab (Humira) in healthy adult subjects

4.1.1.1. Objectives

Primary objective

To demonstrate bioequivalence (as assessed principally by area under the serum concentration-time curve (AUC) from time 0 extrapolated to infinity (AUC_{inf}) and the maximum observed serum concentration (C_{max})) of ABP 501 following a 40 mg subcutaneous (SC) injection relative to that from a 40 mg SC injection of adalimumab (US) and adalimumab (EU).

Secondary objective

To determine the safety, tolerability, and immunogenicity of ABP 501 in healthy adult subjects compared with adalimumab (US) and adalimumab (EU).

Methodology

*Design***:** Phase 1, single-blind (subjects blind), randomised, parallel group study in healthy adult male and female subjects undertaken in two clinical pharmacology units (CPUs) (one in the US (Omaha, Nebraska) and one in the EU (Belfast, Northern Ireland)).

Entry criteria: consent form signed; healthy male/female between 18 to 45 years of age inclusive; highly effective birth control method and agreement not to donate sperm during the study plus 4 months; BMI between 18 and 30 kg/m^2, inclusive; normal or clinically acceptable physical examination, clinical laboratory values, ECG, and vital signs; ability to communicate effectively with the study personnel.

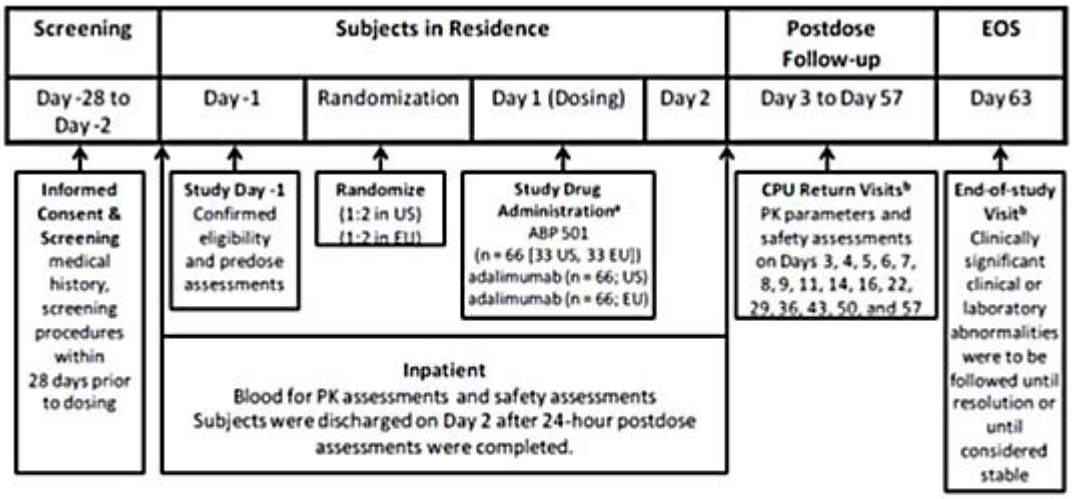
Exclusion criteria: included: lactating women; planned or existing pregnancy; men with pregnant partners; evidence of any infections within the 30 days prior; Evidence of a recent (within 6 months) infection requiring admission or IV antibiotics; previous exposure to TB (if not treated with chemoprophylaxis); TB or fungal infection seen on available chest x-ray taken within 6 months; history of malignancy of any type, other than surgically excised non-melanomatous skin cancers, within 5 years prior to investigational product administration; Positive test for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies; positive screen for alcohol and/or potential drugs of abuse.

*Treatments***:** Each subject received a single dose 40 mg SC injection into the abdomen of ABP 501, adalimumab (US), or adalimumab (EU) in the morning on day 1 following a light, low-fat breakfast.

PK sampling and analysis: A study design and treatment schema is shown in Figure 1. The single dose was given on Day 1. Pharmacokinetic (PK) blood sample (2 mL) collection occurred pre-dose, then 1, 4, 8, 12 and 24 hours post-dose, and then on days 3, 4, 5, 6, 7, 8, 9, 11, 14, 16, 22, 29, 36, 43, 50, 57, and 63 post-dose. The serum concentration of adalimumab was determined using a validated electrochemiluminescent assay. The lower limit of quantification (LLOQ) was 50 ng/mL.

Pharmacokinetic parameters (C_{max}, last measurable serum concentration (C_{last}), time at which C_{max} was observed (t_{max}), AUC from time 0 to the last quantifiable concentration (AUC_{last}), AUC_{inf}, terminal elimination half-life ($t_{½}$), and the terminal elimination rate constant (λ_z)) were calculated from serum adalimumab and ABP 501 concentration data using non-compartmental methods.

Figure 1: Study 20110217 design and treatment schema



Abbreviations: CPU = clinical pharmacology unit; EOS = end-of-study (visit); PK = pharmacokinetic

a. Planned subcutaneous dose: ABP 501 40 mg, adalimumab (US) 40 mg, or adalimumab (EU) 40 mg.
b. Subjects returned to the CPU for collection of blood for PK as close to the nominal time point as possible. Tolerance windows for return visits to the CPU and the EOS visit were consistent with tolerance windows for PK samples on these days (refer to Table 9.3).

Statistical Analysis Plan (SAP): An analysis of covariance (ANCOVA) was used for statistical analysis. Weight and region were used as a covariate in the ANCOVA model for comparison of PK parameters.

Subgroup/sensitivity analyses: The following subgroup analyses of AUC_{last}, AUC_{inf}, and C_{max} were conducted (all on the PK Parameter Population (all subjects with an evaluable adalimumab or ABP 501 serum-concentration time profile)):

Safety analyses: The Safety Population consisted of all subjects who received any amount of investigational product. TEAEs (including ADAs and investigation results) were classified as per MedDRA, analysed, and summarised.

Study participants

- Enrolled: N = 203
- Completed: N = 196 (7 subjects did not complete the study; 4 of those were replaced)
- Analysed: N = 203

PK Results; primary analysis

Overall, the bioequivalence criteria for ABP 501 were met (for both reference products: adalimumab (US) and adalimumab (EU)).

The concentration-time profiles (linear and semi-logarithmic) comparing ABP 501, adalimumab (US), and adalimumab (EU) are shown in Figure 2.

Figure 2: Concentration-time profiles (linear and semi-logarithmic) comparing the geometric means (+SD) of each treatment group of ABP 501, adalimumab (US), and adalimumab (EU)

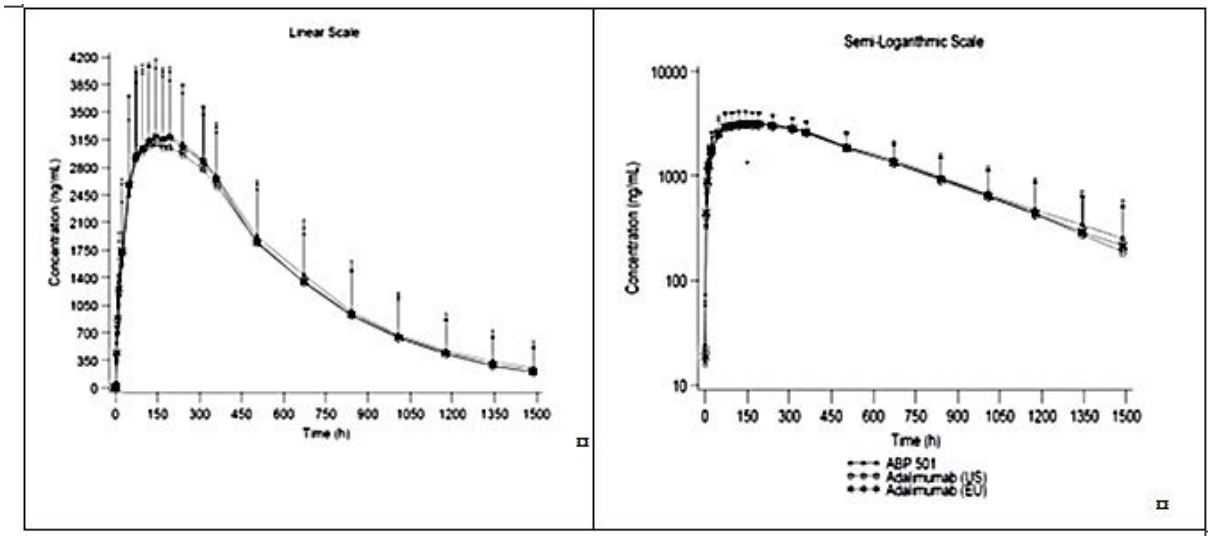


Table 5 contains an overview of the main results, namely the comparison of geometric mean pharmacokinetic parameter ratios (C_{max}, AUC_{inf}, AUC_{last}) and corresponding 90% CIs for the primary analysis.

Table 5: Study 20110217: Comparison of geometric mean pharmacokinetic parameter ratios (C_{max}, AUC_{inf}, AUC_{last}) and corresponding 90% CIs in the primary analysis.

Ratio	ABP 501 vs adalimumab (US)	ABP 501 vs adalimumab (EU)
C_{max} ratio	1.04 (0.964, 1.12)	0.96 (0.889, 1.03)
AUC_{inf} ratio	1.11 (1.00, 1.24)	1.04 (0.935, 1.17)
AUC_{last} ratio	1.07 (0.964, 1.18)	1.07 (0.964, 1.18)

When comparing ABP 501 to adalimumab (US), C_{max}, AUC_{inf}, AUC_{last} were, on average, 3%, 7%, and 3% higher respectively, in ABP 501 subjects. When comparing ABP 501 to adalimumab (EU), C_{max}, AUC_{inf}, AUC_{last} were, on average, 4% lower, 9% higher, and 3% higher respectively, in ABP 501 subjects.

The AUC_{inf} ratio 90% CIs (for ABP 501 vs Adalimumab (US) and ABP 501 vs Adalimumab (EU) were contained by the accepted CI range (0.8 to 1.25) in the whole PK Parameter Population. This satisfies the requirement for bioequivalence.

GeoCV% values were calculated for C_{max}, AUC_{inf}, AUC_{last}. They were above 30% (range 30.2% to 41.7%) in all groups (ABP 501, adalimumab (EU), adalimumab (US).

PK results – subgroup analyses

Some planned subgroup analyses were not performed, as there were no outliers and the Per-protocol PK Parameter Population matched the general population (as per sponsor Table 14.1.3 [not included here]). Furthermore, analysis by region was used in the primary analysis. Consequently, no analyses were conducted for those subgroups.

Table 6: Study 20110217: Comparison of geometric mean pharmacokinetic parameter ratios (C_{max}, AUC_{inf}, AUClast) and corresponding 90% CIs in subgroup analyses (protein content adjustment, antibody status)

Adjustment for protein content	Ratio	Antibody status	ABP 501 vs adalimumab (US)	ABP 501 vs adalimumab (EU)
Unadjusted for protein content	C_{max} ratio	All subjects	1.04 (0.964, 1.12)	0.96 (0.889, 1.03)
		Ab negative subjects	1.05 (0.947, 1.16)	0.98 (0.875, 1.09)
	AUC_{inf} ratio	All subjects	1.11 (1.00, 1.24)	1.04 (0.935, 1.17)
		Ab negative subjects	1.19 (1.03, 1.37)	1.01 (0.865, 1.18)
	AUC_{last} ratio	All subjects	1.07 (0.964, 1.18)	1.07 (0.964, 1.18)
		Ab negative subjects	1.12 (0.988, 1.27)	0.97 (0.844, 1.11)
Adjusted for protein content* **results excluded due to inadequate methodology; shown for completeness only*	C_{max} ratio	All subjects	1.08 (1.00, 1.16)	1.07 (0.989, 1.15)
		Ab negative subjects	1.09 (0.985, 1.21)	1.09 (0.974, 1.22)
	AUC_{inf} ratio	All subjects	1.16 (1.04, 1.29)	1.16 (1.04, 1.30)
		Ab negative subjects	1.24 (1.07, 1.43)	1.13 (0.962, 1.32)
	AUC_{last} ratio	All subjects	1.11 (1.00, 1.23)	1.10 (0.993, 1.22)
		Ab negative subjects	1.16 (1.03, 1.32)	1.08 (0.939, 1.24)

Table 6 contains an overview of the subgroup analyses, namely the comparison of geometric mean pharmacokinetic parameter ratios (C_{max}, AUC_{inf}, AUC_{last}) and corresponding 90% CIs in different subgroups that generated results:

- *Negative antidrug antibody status*: Two of the Ab negative subject subgroup PK parameter ratio 90% CIs were not contained by the accepted CI range limits (highlighted in red in Table 6), namely the AUC_{inf} ratio and the AUC_{last} ratio at 1.19 (1.03, 1.37) and 1.12 (0.988, 1.27) respectively.
- The PK parameter data adjusted for serum protein content are also shown in Table 6 for completeness, but were excluded due to inadequate methodology in generating them.

Comment:

- *Design*: The parallel group design is acceptable, given the long half-life and the risk of immunogenicity. The inclusion and exclusion criteria are acceptable. The use of one strength is acceptable in a drug displaying linear pharmacokinetics.
- *Blinding* The study was single-blind (subjects were blind). This is suboptimal. Furthermore, allocation concealment was not discussed.
- *Unknown subject replacement method*: 4 of the 7 subjects that did not complete the study were replaced by the study investigators. It is unclear which method was employed for that purpose.

- *Dosing:* This was a single-dose study only. Analyses of bioequivalence at steady state during the maintenance phase were not possible. Results from the clinical equivalence studies allowed a comparison of steady state PK.
- *PK sampling and analysis*: was acceptable. Regarding sampling windows, there was no information given whether the actual sampling time was recorded and whether this was sufficiently considered in the data analysis.
- *Statistical methods*: The statistical methods used are compliant with TGA regulatory guidance.
- *Summary on methodology*: The methodology has minor deficiencies (for example, single-blinding, single dosing only), and not all of the methods used have been described in sufficient detail (for example, allocation concealment, subject replacement methods). However, the methodology of the study is acceptable overall. The PK parameter data adjusted for serum protein content were excluded from analysis due to inadequate methodology in generating them, but advice on the issue may be sought from the quality evaluator.
- *Results:* The geometric mean pharmacokinetic parameter ratios (C_{max}, AUC_{inf}, AUC_{last}) comparing ABP 501 to either adalimumab (US) and adalimumab (EU) form the basis of the bioequivalence assessment.
- *Main result:* With regard to the complete patient population (subjects with and without ADAs combined), the results (unadjusted for protein content) support bioequivalence of ABP 501 to both reference products tested (adalimumab (US) and adalimumab (EU)). The geometric mean pharmacokinetic parameter ratios (C_{max}, AUC_{inf}, AUC_{last}) and corresponding 90% CIs for the primary analysis were contained within the reference range (0.8 to 1.25).
- *Comments on the subgroup analyses*:
  - Subgroup analysis by region: the primary analysis matched the subgroup analysis by region, as the comparison of ABP 501 to adalimumab (US/EU) was not pooled, but ABP 501 was compared to adalimumab (US) and adalimumab (EU) separately. The mean PK parameter ratios were within the required interval (0.8 to 1.25) in both groups independently.
  - Subgroup analysis by negative antidrug antibody status: as expected, the PK parameter values in ADA negative subjects were higher compared to the values the total population. When comparing ABP 501 to adalimumab (EU), the mean PK parameter ratios were within the required interval (0.8 to 1.25). When comparing ABP 501 to adalimumab (US), the C_{max} ratio was within the required interval (0.8 to 1.25), but the AUC_{inf} and AUC_{last} ratios were outside the accepted bounds (1.19 (1.03, 1.37) and 1.12 (0.988, 1.27) respectively).
- *Sensitivity analysis by protein content:* A subgroup analysis after adjustment for serum protein content was originally planned by the sponsor and abandoned after the LPLV date. The sponsor stated that due to the nature of nonlinearity in absorption and elimination after subcutaneous administration of adalimumab, a simple linear protein content correction of PK parameters would not have been appropriate.
- It is documented in the reference product PI document that adalimumab exhibits linear pharmacokinetics over the dose range of 0.5 to 10 mg/kg following a single intravenous dose. However, in subcutaneous administration, the pharmacokinetics may not necessarily be linear. Furthermore, SC administration adds more variability, as absorption, distribution, and elimination would be different and would be dependent on individual patient characteristics (for example, sex and age) (Ternant *et al.*, 2015). Inter-individual variability (between-subject variability) was measured in Study 20110217. The GeoCV% values were

above 30% (range 30.2 to 41.7%) for all parameters for which a CV value was calculated (C_{max}, AUC_{inf}, AUC_{last}). The values were similar for ABP 501 and adalimumab (US/EU). Intra-individual variability (within-subject variability) was not measured, but a PK study in Crohn's disease patients over 28 weeks suggests this to be relatively stable (Lie *et al.*, 2014).

- The unadjusted PK parameter results are preferred over a simple linear adjustment for serum protein content, and only the unadjusted results should be considered. The originally proposed method for protein adjustment may not have produced results that are easily comparable to other bioequivalence studies of PK studies in general. The use of unadjusted PK parameter results is consistent with current regulatory practice with regard to similar PK bioequivalence studies for comparable biosimilars with a relatively large inter-individual variability and a relatively wide therapeutic window.
- *Summary comment:* Overall, the bioequivalence criteria for ABP 501 were met. The parameters assessed are within the prescribed bioequivalence margins and support bioequivalence. The serum protein adjusted PK parameter results were excluded from analysis.

4.1.2. Study 20120262

- A Phase III, double-blind, randomised, active comparator-controlled study in 526 subjects with moderate to severe rheumatoid arthritis with concomitant methotrexate and oral corticosteroid use evaluating the efficacy and safety of ABP 501 compared with adalimumab (US).

Supportive PK data was supplied by Study 20120262. One of the exploratory objectives was to assess the trough serum concentration for ABP 501 compared with adalimumab.

The study methods (other than for the purpose of measuring PK trough data) are described in detail in section Efficacy below. Pharmacokinetic samples were taken on Day 1, and then at Weeks 2, 4, 8, 12, 24, and 26.

The Pharmacokinetic Analysis Set consisted of the subset of subjects in the safety analysis set who had at least one evaluable result for serum concentration of ABP 501 or adalimumab (including results below the level of detection): N = 526 (264 subjects in the ABP 501 group and 262 subjects in the adalimumab group). However, as the study progressed, the number of subjects who provided results decreased. Pharmacokinetic concentration data from subjects were analysed according to the actual treatment received.

The 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, but the inter-individual variability was rather large (Table 7).

Table 7: Study 20120262: Geometric mean summary of trough serum pharmacokinetics concentrations (ng/mL) by visit and treatment (Pharmacokinetic Analysis Set)

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.

4.1.3. Study 20120263

- A Phase III, double-blind, randomised, active comparator-controlled study in 350 subjects with moderate to severe psoriasis with no concomitant medications allowed for the treatment of psoriasis evaluating the efficacy and safety of ABP 501 compared with adalimumab (EU).

Supportive PK data was supplied by Study 20120263. One of the exploratory objectives was to assess the trough serum concentration for ABP 501 compared with adalimumab.

The study methods (other than for the purpose of measuring PK data) are described in detail in section Efficacy below. Pharmacokinetic samples were taken on Day 1, and then at Weeks 4, 16, 20, 32, and 52.

The Pharmacokinetic Analysis Set consisted of the subset of subjects in the safety analysis set who had at least one evaluable result for serum concentration of ABP 501 or adalimumab (including results below the level of detection): N=347 (initially 174 subjects in the ABP 501 group and 173 subjects in the adalimumab group; in the re-randomised group: 152 subjects (Group A: ABP 501/ABP 501); 79 subjects (Group B1: adalimumab/adalimumab); 77 subjects (Group B2: adalimumab/ABP 501). However, as the study progressed, there was a small amount of subject attrition. Pharmacokinetic concentration data from subjects were analysed according to the actual treatment received.

From baseline to Week 16, the geometric mean trough serum concentrations were similar between Treatment Group A (ABP 501) and Treatment Group B (adalimumab) (Table 8).

Table 8: Study 20120263: Geometric mean summary of trough serum pharmacokinetics concentration (ng/mL) by visit and treatment, Baseline to Week 16 (Pharmacokinetic Analysis Set)

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.
Source Dataset: ADPK, Program: t_gmpk.sas, Output: t14-09-003-pk-sum-pk.rtf, Generated on: 22MAY2015 08:42

From baseline to the end of study, the geometric mean trough serum concentrations were similar between the re-randomised treatment groups for most time points (Table 9). The inter-individual variability was rather large, especially from Week 16 onwards.

Table 9: Study 20120263: Geometric mean summary of trough serum pharmacokinetics concentrations (ng/mL) by visit and treatment group; Baseline to end of study (Pharmacokinetics Analysis Set).

	Re-randomized		
Timepoint	Treatment Group A (ABP 501/ ABP 501) (N = 152)	Treatment Group B1 (Adalimumab/ Adalimumab) (N = 79)	Treatment Group B2 (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.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries.

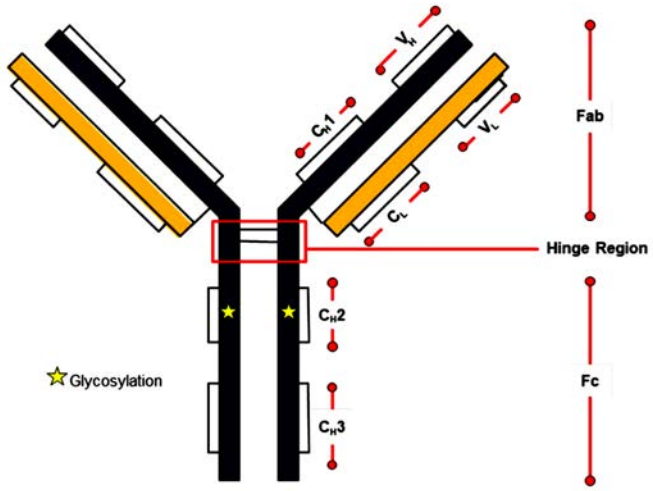
ABP 501 is a fully human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass expressed in Chinese hamster ovary cells. It specifically binds to human tumor necrosis factor α (TNFα) and prevents it from binding to TNFα receptor 1 (TNFR1, p55TNFR, or TNFRSF1A) and TNFα receptor 2 (TNFR2, p75TNFR, or TNFRSF1B).

ABP 501 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 disulphide bonds. Each HC contains 451 amino acids with 4 intrachain disulphides. Each LC contains 214 amino acids with 2 intrachain disulphides. Each HC contains an N-linked glycan at the consensus glycosylation site on Asn^{301}.

The molecular formula for the predominant ABP 501 HC isoform (C-terminal glycine) is $C_{2191}H_{3392}N_{582}O_{677}S_{15}$ (not including N-linked glycans). The theoretical mass of glycosylated ABP 501 containing 2 N-linked glycans (1 per HC) is 148,081 Da (experimentally determined predominant ABP 501 mass: 148,083 Da). Important physicochemical characteristics are summarised in Table 10.

A schematic diagram of ABP 501 has been provided by the sponsor and is reproduced in Figure 3.

Figure 3: Schematic structure of ABP 501 (Amgevita (adalimumab))



Heavy chains are shown in blue and light chains are shown in orange.
Black lines represent disulfide bonds.
V_H is the variable domain of the heavy chain.
C_H1, C_H2, and C_H3 are the constant domains of the heavy chain.
V_L is the variable domain of the light chain.
C_L is the constant domain of the light chain.

Table 10: Physicochemical characteristics of ABP 501

Property	Results
Immunoglobulin subclass	IgG1
Biological target	Specific binding to tumor necrosis factor α
Molecular mass[a]	145,194 Da for deglycosylated molecule 148,083 Da including glycosylation (major)
Cysteines	32
Number of disulfide bonds	16
Glycosylation	N-linked: Asn^{301} at each heavy chain
Extinction coefficient	Theoretical: 1.46 $cm^{-1}(mg/mL)^{-1}$ at A_{280} Experimental: 1.39 $cm^{-1}(mg/mL)^{-1}$ at A_{280}
Isoelectric point (pI)	Theoretical: 8.7 Experimental: 8.5 (main species)
T_m (melting temperatures)[a]	T_{m1} = 74°C (C_H2 and Fab) T_{m2} = 85°C (C_H3)

[a] Experimentally determined

The sponsor states that, based on a comprehensive analytical similarity assessment, ABP 501 is analytically similar to the reference product, and has the same primary amino acid sequence and the same strength as the reference product.

4.2.2. Pharmacokinetics in healthy subjects and the target population

The following information on pharmacokinetics is derived from the proposed product information (PI) document for ABP 501 (Amgevita) and refers to the reference product Humira. The section with regard to pharmacokinetics is identical to the corresponding section in the reference product PI document, except for minor formatting changes and a statement that Amgevita is pharmacokinetically similar to Humira.

Healthy volunteers and patients with RA on adalimumab had similar pharmacokinetic profiles.

No PK studies have examined the effects of food, the administration timing, or the use in patients with renal or hepatic impairment.

4.2.2.1. Absorption

Humira is administered subcutaneously and absorbed relatively slowly. In a study with 59 healthy adult subjects, mean peak serum concentration was reached about five days after administration. Based on three studies following a single 40 mg subcutaneous dose, the average absolute bioavailability of Humira was estimated to be 64%. Humira demonstrated linear pharmacokinetics over the dose range of 0.5 to 10 mg/kg following a single intravenous dose.

4.2.2.2. Distribution

In single-dose studies with rheumatoid arthritis (RA) patients given intravenous doses ranging from 0.25 to 10 mg/kg, the volume of distribution at steady state (V_{SS}) was found to be between 4.7 and 6.0 L. Humira concentrations in the synovial fluid from five RA patients ranged from 31 to 96% of concentrations in serum.

4.2.2.3. Excretion

Humira is slowly eliminated, with clearances typically under 12 mL/h. The mean terminal phase half-life (t½) was approximately two weeks, ranging from 10 to 20 days across studies. The mechanism and route of elimination remain unknown, but it is expected that adalimumab is degraded into smaller peptides and amino acids via catabolic pathways/proteolytic degradation in a similar fashion to endogenous immunoglobulins.

Inter-individual variability

The following information on inter-individual variability (between subject variability; as indicated by a coefficient of variance (in %)) of pharmacokinetics was provided in the dossier of this application, but relates to data generated for Humira.

In a single-dose bioequivalence study of 40 mg SC adalimumab, the post-dose inter-individual variability was found to be 27.7% (AUC (time 0-360h)) and 33% (C_{max}) for the market formulation.

In a different relative bioavailability study with 16 subjects per treatment group, a single dose of 40 mg of 3 injectable formulations of adalimumab were compared. The post-dose inter-individual variability was found to be 25.2% (AUC (time 0-360h)), 24.9% (AUC_{last} (all subjects)), 21.1% (AUC_{last} with non-measurable human anti-human antibodies), and 8.1% (AUC_{inf}).

The inter-individual variability (between-subject variability) data was a parameter used for the sample size calculation of Study 20110217 using an assumption of inter-individual variability of 38% to account for potential sources of variability for ABP 501, adalimumab (US), and adalimumab (EU).

Intra-individual variability

High inter-individual variability (between-subject variability) does not necessarily imply high intra-individual variability (within-subject variability).

The following information on intra-individual variability (within subject variability) of pharmacokinetics was sourced from the literature and relates to Humira in Crohn's disease (Lie *et al.*, 2014):

> *A retrospective cohort study with 76 patients with Crohn's disease found that intra-individual adalilumab levels seemed stable during the study period (28 weeks), whereas inter-individual levels varied. However, in drugs with a long half-life relative to the dosing interval, intra-individual variability in AUC is likely to be reduced when measured at steady state.*

4.2.3. Pharmacokinetic interactions

Only interactions between Humira and methotrexate have been evaluated in formal pharmacokinetic studies (see below).

4.2.3.1. Methotrexate

In a study with 21 RA patients on stable methotrexate therapy, there were no statistically significant changes in the serum methotrexate concentration. However, methotrexate reduced Humira's apparent clearances by 29% (single dosing) and 44% (multiple dosing).

4.3. Evaluator's overall conclusions on pharmacokinetics

Overall, the bioequivalence criteria for ABP 501 were met. The main results were within the prescribed bioequivalence margins and are acceptable. The serum protein adjusted PK parameter results were excluded from analysis.

Overall, the clinical efficacy studies support the results of the PK bioequivalence study.

Humira is currently approved in Australia and its PK study data and their description in the product information (PI) document have previously been accepted by the TGA. Consequently, the product information (PI) document of any approved biosimilar to Humira without separate PK studies should contain the identical information with regard to pharmacokinetics. The proposed PI document for Humira fulfils this requirement.

5. Pharmacodynamics

No studies providing pharmacodynamics information were submitted with this application.

Pharmacodynamic data pertaining to Humira are proposed to be included in the Amgevita PI. In the proposed PI for Amgevita, the section with regard to pharmacodynamic data is identical to the corresponding section in the reference product PI document.

6. Dosage selection for the pivotal studies

The doses used in both clinical equivalence studies were identical to the recommended dosing regimen for the respective indications in the reference product Humira.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

The following two studies provided evaluable efficacy data:

7.1.1. Rheumatoid arthritis

Study 20120262: a Phase III, double-blind, randomised, active comparator-controlled study in 526 subjects with moderate to severe rheumatoid arthritis with concomitant methotrexate and oral corticosteroid use evaluating the efficacy and safety of ABP 501 compared with adalimumab (US).

7.1.2. Psoriasis

Study 20120263: a Phase III, double-blind, randomised, active comparator-controlled study in 350 subjects with moderate to severe psoriasis with no concomitant medications allowed for the treatment of psoriasis evaluating the efficacy and safety of ABP 501 compared with adalimumab (EU).

7.2. Indication: Rheumatoid arthritis

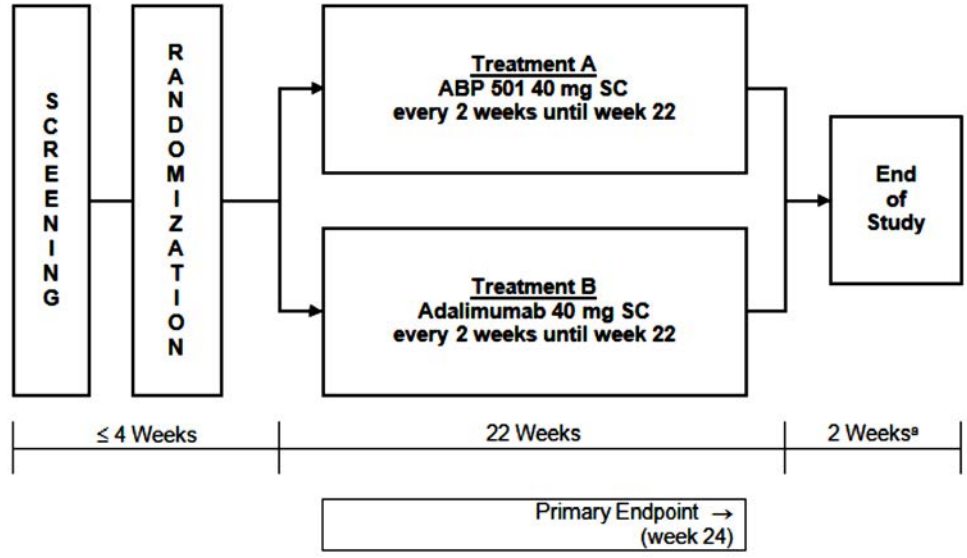
7.2.1. Pivotal or main efficacy study: Study 20120262

7.2.1.1. Study design, objectives, locations and dates

Design

Study 20120262 was a Phase III, double-blind, parallel-group, randomised, active comparator-controlled, comparative equivalence trial in 526 adalimumab-naïve subjects with moderate to severe rheumatoid arthritis with concomitant methotrexate (but inadequate response to it) and oral corticosteroid use evaluating the efficacy and safety of ABP 501 compared with adalimumab (US).

Figure 4: Study 20120262: Study design schema.



SC = subcutaneous
[a] Additional safety follow-up

The outline of the study design is shown in Figure 4. The total duration of the study was up to 30 weeks:

- *Screening period*: Subjects were screened and randomised up to 4 weeks before drug administration.
- *Administration period*: Subjects received either ABP 501 or adalimumab at 40 mg subcutaneous (SC) every 2 weeks until week 22. The primary endpoint was assessed at Week 24.
- *End of study period*: Safety follow-ups occurred up to week 26 (end of study date).

Objectives

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

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

Exploratory objectives: The exploratory objectives were to assess the following:

- Injection site pain perception based on subject's rankings for ABP 501 compared with adalimumab.
- Trough serum concentration for ABP 501 compared with adalimumab.

Location and dates

The study was conducted at 92 sites in 12 countries (in Europe and North America) between 24 October 2013 (first subject enrolled) and 19 November 2014 (last subject completed study).

Comment: Only 72 sites are listed in Appendix 16.1.4 of the CSR.

7.2.1.2. Inclusion and exclusion criteria

The main inclusion criteria included:

- Men and women ≥ 18 to ≤ 80 years of age.
- Diagnosed with RA (2010 ACR or EULAR criteria for RA moderate to severe RA) for at least 3 months.

- Active RA defined as ≥ 6 swollen joints and ≥ 6 tender joints at screening and baseline and at least 1 of the following at screening: ESR ≥ 28 mm/hr or serum CRP > 1.0 mg/dL.
- Positive for RF or Anti-CCP at screening.
- Received MTX for ≥ 12 consecutive weeks, and on a stable dose of 7.5 to 25 mg per week for ≥ 8 weeks before receiving investigational product. Subjects must be willing to remain on stable dose of MTX throughout the study.

The main exclusion criteria included:

- Prior use of 2 or more biological therapies for RA, Humira (adalimumab), or a biosimilar of adalimumab.
- Active, recurrent, or chronic infections, history of serious infections (including HIV, HBV, HCV, and TB).
- Uncontrolled clinically significant systemic disease, NYHA III/IV heart failure, or another potentially interfering disease (including CNS demyelinating disease, chronic inflammatory disease, or connective tissue disease.
- History of malignancy within 5 years (except cured cutaneous SCC, BCC, in situ cervical cancer, or in situ breast ductal carcinoma).
- Hypersensitivity to any active or excipient.
- Laboratory abnormalities (Hb < 9 g/dL; platelets < 100,000/mm^3; white blood cell count < 3,000 cells/mm^3; AST and ALT > 2 x ULN; creatinine clearance < 50 mL/min (Cockroft-Gault formula); any other potentially interfering abnormality).
- Other exclusions: substance abuse (including high potency analgesics), pregnancy, breast feeding, absence of adequate contraception, planned surgical procedures, or inability to comply with the study procedures.

Comment: The inclusion and exclusion criteria that were used in the study are acceptable. Furthermore, they provide a reasonable balance between internal and external validity.

7.2.1.3. Study treatments

Subjects received either ABP 501 40 mg SC or adalimumab 40 mg SC on Day 1 and every 2 weeks (± 3 day dose window, for example, in case of infection) until week 22. A missed dose or a dose delayed for more than 3 days was not given, and the subsequent dose given according to the original schedule.

All subjects continued on a stable dose of methotrexate (MTX) (≥ 7.5 mg/week, oral, or SC) (unless side effects required a lower dose), except for one subject in the ABP 501 group that was excluded from the PP analysis, as the subject also had a negative RF and anti-CCP result. The following other concomitant medications were allowed:

- Oral corticosteroids at a dose of ≤ 10 mg prednisone (or equivalent) per day (if the subject was at a stable dose for 4 weeks or more prior to initiation of study treatment.
- Non-live vaccinations.

Rescue medications not affecting RA (for example, oral corticosteroids, paracetamol, NSAIDs, COX-2 inhibitors) were allowed under certain conditions (outlined in the study protocol).

Comment: The dosing schedule and rules were appropriate, as they were identical to the dosing recommendation for the reference product. The choice of comparator was appropriate, as Humira is accepted as the innovator product in Australia. The rescue medication rules were more restrictive than the rules in the originator trial

(Keystone *et al.*, 2004) and therefore less likely to affect the internal validity of the study.

7.2.1.4. Efficacy variables and outcomes

ACR score

For the purposes of this study, the ACR core set measurements for rheumatoid arthritis were used (as outlined in the Clinical Study Protocol for Study 20120262).

ACR Core Set Measurements:

- tender joint count
- swollen joint count
- Subject's Global Health Assessment
- Investigator's Global Health Assessment
- Subject's assessment of pain
- Health Assessment Questionnaire – Disability Index (HAQ-DI)
- CRP

The joints to be assessed for tenderness (68 joints) and swelling (66 joints) consisted of the following:

- temporomandibular joint
- sternoclavicular joint
- acromioclavicular joint
- shoulders*
- elbows*
- wrists*
- interphalangeal on digit 1*
- distal interphalangeal joints on digits 2 to 5
- proximal interphalangeal joints on digits 2 to 5*
- metacarpophalangeal joints on digits 1 to 5*
- hips (tenderness only)
- knees*
- ankles
- metatarsals
- interphalangeal joints on toes 1 to 5
- metatarsophalangeal joints on toes 1 to 5

Joints assessed for swelling are the same, with the exception of the hips, which are excluded.

* The 28 joints used to calculate the DAS28.

Primary efficacy variable (endpoint)

The primary efficacy endpoint was the risk ratio (RR) of ACR20 at Week 24. 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 (symptom-free and no arthritis symptoms) to 10 (maximum arthritis disease activity) horizontal scale)
- Investigator's Global Health Assessment (on a 0 (symptom-free and no arthritis symptoms) to 10 (maximum arthritis disease activity) horizontal scale)
- Subject's assessment of pain (on a 100-mm visual analogue scale (VAS) from 'no pain at all' to 'worst pain imaginable')
- Health Assessment Questionnaire - Disability Index (HAQ-DI) (range: 0 to 3)
- Serum CRP concentration

Secondary efficacy variables (endpoints)

Secondary efficacy endpoints included:

- Change from baseline of the Disease Activity Score 28-CRP (DAS28-CRP) at each time point (Weeks 2, 4, 8, 12, 18, and 24)
- RR of ACR20 responses at Weeks 2 and 8
- RR of ACR50 (50% improvement in ACR core set measurements) and ACR70 (70% improvement in ACR core set measurements) responses at Week 24

Comment: The efficacy variables used were in accordance with EU guidance 'Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for treatment of Rheumatoid Arthritis' (CPMP/EWP/556/95 rev 1/Final, 2003). In particular, ACR20, ACR50, and ACR70 are validated indicators in rheumatoid arthritis that had been used in the originator trial (Keystone *et al.*, 2004) with ACR20 after 24 weeks being one of the three primary endpoints.

7.2.1.5. Randomisation and blinding methods

Randomisation

Patients were randomly assigned in a 1:1 ratio to receive either ABP 501 or adalimumab. Randomisation was computer-generated prior to the commencement of the study. The scheme was prepared by a statistician not involved in the study in a blinded fashion using an interactive voice or web response system (IXRS).

Randomisation was stratified by geographic region (Eastern Europe, Western Europe, North America/Latin America) and prior biological use for RA (with prior biological use capped at 40% of the study population).

Blinding

The following were blinded until the end of the study period:

- Subjects
- All personnel involved with the conduct and the interpretation of the study (including investigators, study centre personnel, and sponsor staff).

ABP 501 and adalimumab were provided in prefilled, indistinguishable syringes which were dispensed by the IXRS. However, in an emergency, the treatment assignment could have been retrieved through the IXRS.

Allocation concealment

Allocation concealment was not specifically discussed.

Comment: The randomisation and blinding methods were adequate.

7.2.1.6. Analysis populations

The analysis populations consisted of the following:

- *Full Analysis Set*: consisted of all subjects randomised in the study (based on intention to treat principle). This set was used to perform the primary efficacy analysis.
- *Per-protocol Analysis Set:* a subset of the Full Analysis Set which included subjects who completed the treatment period and did not have a protocol violation that would affect evaluation of the primary objective of the study. This set was used for sensitivity analyses of the key efficacy endpoints.
- *Safety Analysis Set:* The safety analysis set included all randomised subjects who received at least one dose of investigational product. In this study, it appears to be identical to the Full Analysis Set.
- *Antidrug Antibody Analysis Set:* consisted of the subset of subjects in the safety analysis set who had at least one evaluable antibody test result (to either ABP 501 or adalimumab). Immunogenicity data from subjects were analysed according to the actual treatment received.
- *Pharmacokinetic Analysis Set:* consisted of the subset of subjects in the safety analysis set who had at least one evaluable result for serum concentration of ABP 501 or adalimumab (including results below the level of detection). Pharmacokinetic concentration data from subjects were analysed according to the actual treatment received.

Comment: The primary efficacy analysis was conducted using the intention-to-treat (ITT) population (Full Analysis Set) and is the preferred method for superiority trials. There is no overall consensus on whether intention-to-treat population (ITT) or per-protocol (PP) population is preferable for equivalence trials. ITT analyses often tend to bias the results toward equivalence. The preferred method is to provide analyses of both ITT and PP population sets, and the sponsor has done so at least for the key efficacy endpoints. The main analysis population matched the population specified in the study protocol.

7.2.1.7. Sample size

For determination of equivalence between ABP 501 and adalimumab treatment groups based on the primary endpoint (ACR20 RR at Week 24), a sample size of approximately 500 subjects was calculated based on the following assumptions:

- Expected ACR20 response for both ABP 501 and adalimumab of 63% at Week 24.
- 1:1 randomisation (ABP 501: adalimumab).
- Power > 90%.
- Equivalence margin of (0.738, 1/0.738) with a 2-sided significance level of 0.05.
- Dropout proportion of 15% by Week 24.

Furthermore, the determined sample size for the primary endpoint was expected to provide > 90% power to demonstrate equivalence between the ABP 501 and adalimumab treatment 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).

Comment: The assumptions used for determining the sample size are acceptable.

7.2.1.8. Statistical methods

Inferential analyses were conducted for the primary endpoint, and descriptive analyses for secondary endpoints and safety endpoints. All endpoints had descriptive summaries: the categorical variable results were shown using the number and per cent of subjects in each category; the continuous variable results were shown using mean, standard deviation, median, minimum, maximum, and number of subjects with observations. The 'Last Observation Carried Forward' method was used to accommodate missing data.

Primary endpoint

The primary endpoint was the RR of ACR20 between ABP 501 and adalimumab at Week 24. The study hypothesis was that there were no clinically meaningful differences (that is, clinical equivalence) between ABP 501 and adalimumab with regard to the primary endpoint. This was evaluated by comparing the 2-sided 90% confidence interval (CI) of the primary endpoint with a pre-specified equivalence margin of (0.738, 1/0.738). The 90% CI and 95% CI were estimated using a generalised linear model (a log-binomial regression model). Covariates were treatment and stratification factors.

Secondary endpoints

Secondary efficacy endpoints were the change from baseline of the DAS28-CRP at each time point, RR of ACR20 responses at Weeks 2 and 8, and RR of ACR50 and ACR70 responses at Week 24.

Treatment differences regarding the DAS28-CRP change for all time points from baseline were evaluated with a repeated-measures analysis. Apart from stratification variables, visit (week), treatment group, treatment-by-visit interactions, and baseline DAS28-CRP were included in the model. 90% and 95% CIs were determined for mean difference of DAS28-CRP change from baseline between ABP 501 and adalimumab at each time point.

The RR of ACR20 at Weeks 2 and 8, and the RRs of ACR50 and ACR70 at Week 24 were summarised descriptively with corresponding 90% and 95% CIs for RR and risk difference (RD) having been estimated using the generalised linear model adjusted for stratification factors.

Safety endpoints

Safety endpoints were summarised descriptively. Subgroup analyses (by age, race, sex, and other stratification factors) were also provided.

Primary endpoint equivalence margin

Only a rather short justification for the wide primary endpoint equivalence margin was given in the original dossier submitted to the TGA. The sponsor was invited to provide a more detailed justification for the wide equivalence margin chosen (0.738, 1/0.738) which was provided and is incorporated below.

It is best practice to determine the anticipated treatment effect from historical randomised clinical trials of adalimumab, ideally by using results from meta-analysis of multiple studies. The sponsor has identified relevant studies in a literature review, five of which also used ACR20 as a variable. Three of those studies included patients with previous MTX use (Keystone *et al*., 2004; Weinblatt *et al*., 2003; Kim *et al*., 2007). To determine the equivalence margin, the sponsor chose to use the treatment effect from Keystone *et al*. (2004) only, rather than combined treatment effect from a meta-analysis of the three studies. This was done for mainly two reasons:

- The study in Keystone *et al*. (2004) contained a similar population and was sufficiently large to allow a robust estimate of the treatment effect.
- The equivalence margin derived from the combined treatment effect (three study meta-analysis) would have been wider (0.7054, 1/0.7054).

The equivalence margin was calculated as follows (methodology as suggested by the FDA draft guidance for industry: Non-Inferiority Clinical Trials (March 2010) (FDA, 2010)):

- Using the Keystone *et al*. (2004) study, the point estimate for the ACR20 RR between placebo and adalimumab was determined to be 0.47 (placebo response proportion/adalimumab response proportion = 29.5%/63.3% = 0.47) with an 80% confidence interval of (0.3990, 0.5447). Using a non-inferiority margin based on an 80% confidence interval was deemed appropriate for a biosimilar candidate with demonstrated pharmacologic, analytic and pharmacokinetic similarity.
- The non-inferiority side of the equivalence margin was determined using e (Euler's number) to the power of half of the natural logarithm of the upper 80% confidence bound value ($e^{(0.5)(\ln \text{upper 80\% CI bound})} = e^{(0.5)(\ln 0.5447)} = 0.7380$). Consequently, 0.7380 was used as the lower bound of the equivalence margin, and 1/0.7380 as the upper bound (on a logarithmic scale).

Comment: The sponsor's statistical analysis plan is acceptable. Prior to study commencement, the sponsor amended the protocol to accommodate the request of the German Health Authority to include presentation of 95% confidence intervals (CIs) for efficacy endpoints and to specify the missing data handling procedures. For statistical analysis of equivalence trials, a 95% CI is the preferred option. The sponsor originally only proposed to determine a 90% CI, but has altered the protocol and provided a 95% CI as well. This gives the evaluator the opportunity to analyse the study results based on 95% CI data.

The sponsor's reasoning for using the treatment effect from the clinical trial described in Keystone *et al*. (2004) as a basis for the equivalence margin calculation is acceptable, especially given that said trial was the pivotal efficacy trial for adalimumab (Humira). The methodology for determining the equivalence margin appears reasonable in principle, even though the resulting margin exceeds the usually accepted margin of ± 15%. However, using a margin of ± 15% is the recommended approach.

7.2.1.9. Participant flow

A total of 526 subjects (264 in ABP 501; 262 in adalimumab) were enrolled and randomised in this study and received at least 1 dose of investigational product. 494 of these subjects (93.9%) completed the study. 17 subjects (3.2%) withdrew consent, 10 subjects (1.9%) discontinued study because of other reasons (all related to adverse events), 4 subjects (0.8%) were lost to follow-up, and 1 subject (0.2%) discontinued study due to protocol violations. An overview is shown in Table 11.

Table 11: Study 20120262: Subject study and investigational product disposition by treatment (Full Analysis Set)

Variable	ABP 501 (N = 264) n (%)	Adalimumab (N = 262) n (%)	Total (N = 526) n (%)
Subjects Randomized	264	262	526
Completed Study	243 (92.0)	251 (95.8)	494 (93.9)
Discontinued Study	21 (8.0)	11 (4.2)	32 (6.1)
Reason for Discontinuing Study			
Consent Withdrawn	11 (4.2)	6 (2.3)	17 (3.2)
Other[a]	7 (2.7)	3 (1.1)	10 (1.9)
Lost to Follow-up	2 (0.8)	2 (0.8)	4 (0.8)
Protocol Violations	1 (0.4)	0 (0.0)	1 (0.2)
Subjects Treated with IP	264 (100.0)	262 (100.0)	526 (100.0)
Completed IP	246 (93.2)	250 (95.4)	496 (94.3)
Discontinued IP	18 (6.8)	12 (4.6)	30 (5.7)
Reason for Discontinuing IP			
Consent Withdrawal for Treatment	9 (3.4)	6 (2.3)	15 (2.9)
Adverse Event	6 (2.3)	2 (0.8)	8 (1.5)
Lost to Follow-up	2 (0.8)	2 (0.8)	4 (0.8)
Protocol Violation	1 (0.4)	0 (0.0)	1 (0.2)
Physician Decision	0 (0.0)	1 (0.4)	1 (0.2)
Other[b]	0 (0.0)	1 (0.4)	1 (0.2)

IP = investigational product

[a] All related to adverse events (Listing 16-2.1.1)

[b] Subject discontinued IP because of consent withdrawn because of an adverse event (Listing 16-2.1.1)

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

With regard to analysis sets, the data are as follows:

- Full Analysis Set: N = 526

  Patient group with treatment assignment based on original randomised treatment assignment (rather than actual treatment received) following the intention-to-treat principle.

- Per-protocol Analysis Set: N = 463

  A subset of the Full Analysis Set which included subjects who completed the treatment period and did not have a protocol violation that would affect evaluation of the primary objective of the study. This set was used for sensitivity analyses of the key efficacy endpoints.

- Safety Analysis Set: N = 526

  The safety analysis set included all randomised subjects who received at least 1 dose of investigational product.

- Antidrug Antibody Analysis Set: Binding Ab N = 201; Neutralising Ab N = 46

  Consisted of the subset of subjects in the safety analysis set who had at least 1 evaluable antibody test result (to either ABP 501 or adalimumab). Immunogenicity data from subjects were analysed according to the actual treatment received.

Comment: The Full Analysis Set followed the ITT principle which constituted the primary analysis set. If too many patients are lost to follow up at 24 weeks, differences between groups could be reduced and equivalence may be falsely concluded. The sponsor has conducted appropriate sensitivity analyses with the Per-protocol Analysis Set for the key efficacy endpoints.

7.2.1.10. Major protocol violations/deviations

55 out of 526 subjects (10.5%) had one or more major protocol violations, and the proportion was reasonably similar in each group (9.5% in the ABP 501 group, and 11.5% in the adalimumab group (Table 12). The most common major protocol violation was mis-stratification at randomisation stage due to incorrect prior biological use designation (4.2% in the ABP 501 group, and 2.3% in the adalimumab group). A summary of major protocol violations is shown in Table 12. A summary of eligibility related protocol violations is shown in Table 13 (a subset of those shown in Table 12).

Table 12: Study 20120262 Major protocol deviations/violations (Full Analysis Set)

Category Deviation/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 ESR/CRP	2 (0.8)	3 (1.1)	5 (1.0)
Prior use of 2 or more biologic therapies	1 (0.4)	2 (0.8)	3 (0.6)
Prohibited non-biologic 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	0 (0.0)	1 (0.4)	1 (0.2)
Violation	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 ESR/CRP	2 (0.8)	3 (1.1)	5 (1.0)
Prior use of 2 or more biologic therapies	1 (0.4)	2 (0.8)	3 (0.6)
Prohibited non-biologic 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	0 (0.0)	1 (0.4)	1 (0.2)

Note: For each category and deviation/violation, subjects are included only once, even if they experienced multiple events in that category or deviation/violation.

Table 13: Study 20120262 Eligibility related protocol deviations/violations (Full Analysis Set)

Deviation/Violation	ABP 501 (N = 264) n (%)	Adalimumab (N = 262) n (%)	Total (N = 526) n (%)
Subjects with at least one eligibility related protocol deviation/violation	11 (4.2)	17 (6.5)	28 (5.3)
Negative RF and Anti-CCP at screening	3 (1.1)	4 (1.5)	7 (1.3)
Laboratory abnormalities at screening	4 (1.5)	2 (0.8)	6 (1.1)
Inappropriate joint count and ESR/CRP	2 (0.8)	3 (1.1)	5 (1.0)
Prior use of 2 or more biologic therapies	1 (0.4)	2 (0.8)	3 (0.6)
Prohibited non-biologic DMARDs	1 (0.4)	2 (0.8)	3 (0.6)
Positive PPD with positive quantiferon, symptoms of TB, or without adequate prophylaxis	0 (0.0)	2 (0.8)	2 (0.4)
Dose of oral corticosteroids not per protocol at study entry	0 (0.0)	1 (0.4)	1 (0.2)
IA, IV, or IM corticosteroids or IA hyaluronic acid injection	0 (0.0)	1 (0.4)	1 (0.2)
Informed Consent not provided	0 (0.0)	1 (0.4)	1 (0.2)

Note: For each deviation/violation, subjects are included only once, even if they experienced multiple events in that deviation/violation.

Comment: To mitigate the potential effect of protocol violations/deviations, the sponsor has conducted appropriate sensitivity analyses with the Per-protocol Analysis Set (which excluded subjects for whom major violations were recorded) for the key efficacy endpoints.

7.2.1.11. Baseline data

Both the demographic and the RA-related baseline characteristic proportions were reasonably balanced between treatment groups (ABP 501 and adalimumab) in the Full Analysis Set, and the per protocol analysis set (N = 463). The safety analysis set appears to be identical to the Full Analysis Set (N = 526).

The following proportions refer to the Full Analysis Set (except for individual prior medication data which refers to the safety analysis set (identical to the Full Analysis Set).

The overall mean age was 55.9 years (range 21 to 80 years) with the majority of subjects being over 65 years of age (76.4%, 402/526). The majority of subjects were female (81.0%, 426/526). The majority of subjects were non-Hispanic Caucasian (88.6%, 466/526).

63.7% of subjects had RA duration of ≥ 5 years (61.7% (ABP 501) and 65.6% (adalimumab). The mean duration was 9.39 years and the median duration was 7.09 years. A positive rheumatoid factor (RF) result was present in 92.0% (243/264) and 91.6% (240/262) in the ABP 501 and adalimumab group respectively. A positive RF *and* positive anti-CCP result was present in 73.5% (194/264) and 80.5% (211/262) in the ABP 501 and adalimumab group respectively.

The DAS28-CRP scores were balanced between groups (DAS28-CRP median score: 5.60 (5.59 versus 5.70).

Baseline ACR scores were not provided. However, the baseline values of the individual components that make up the ACR score were provided (tender joint count; swollen joint count; Subject's Global Health Assessment; Investigator's Global Health Assessment; Subject's assessment of pain; Health Assessment Questionnaire – Disability Index (HAQ-DI); CRP).

The swollen or tender joint counts ware balanced between groups (median swollen joint count: 12.0 in both groups; median tender joint count: 21.0 (21.0 versus 20.5)). The median values for Subject's Global Health Assessment, Investigator's Global Health Assessment, and Health Assessment Questionnaire - Disability Index (HAQ-DI) were identical between groups.

The Subject's assessment of pain was slightly lower in the ABP 501 group (60.0 versus 65.0). The CRP level (mg/L) was slightly lower in the ABP 501 (versus the adalimumab group) group (mean: 13.881 (± 20.6870); median: 6.140 (range 0.12 to 222.10) versus mean: 14.678 (± 19.3848); median: 7.630 (range 0.12 to 147.41)). ESR levels were not given.

The baseline medication status was balanced between treatment groups. 70.7% (372/526) of subjects had used medications before the study (68.9%; 182/264) in the ABP 501 group versus 72.5% (190/262) in the adalimumab group). More than 70% of subjects did not have biological therapy for RA prior to this study, approximately half had been using oral corticosteroids, and more than 60% had been using NSAIDs.

Methotrexate was used in more than 30% (ABP 501 group: 34.8% (92/264), adalimumab group: 34.7% (91/262). The median dose of methotrexate was 15 mg/week for both groups with the range being 7.5 to 25 mg/week (mean: 16.89 mg/week (±4.811) versus mean: 16.56 mg/week (±4.932).

With regard to previous monoclonal antibody use, the differences between groups are reasonably similar, except for the following drugs (ABP 501 group versus adalimumab group): etanercept (4.9% (13/264) versus 8.4% (22/262) and infliximab (1.9% (5/264) versus 3.4% (9/262).

Evaluator comment: The Full Analysis Set which was the set used for the primary analysis by the sponsor was reasonably balanced between treatment groups. Furthermore, the Per-protocol Analysis Set (not shown in the main body of the study report) was also reasonably balanced between treatment groups. The characteristics shown reflect the population of rheumatoid arthritis patients reasonably well (for example, when comparing the study population to the population described in Sany *et al*., 2004, which assessed the characteristics of French RA patients treated by hospital rheumatologists) which is supporting the external validity of the study. Additionally, the demographics were very similar to the pivotal adalimumab trial (Keystone *et al*., 2004). Many parts of the different RA disease scoring systems rely on subjective assessment by both physicians and patients. However, in a large enough sample and

treatment groups with near identical characteristic, the amount of bias would have been adequately mitigated.

There were some small differences in previous monoclonal antibody use between the groups (etanercept and infliximab).

In summary, the baseline data is sufficiently balanced between treatment groups to support internal validity and sufficiently similar to a real-world moderate to severe RA population to support external validity.

7.2.1.12. Results for the primary efficacy outcome

The Full Analysis Set was used for the efficacy analysis set. The Per-protocol Analysis Set was used in a sensitivity analysis for selected key efficacy endpoints (that is, most importantly the primary efficacy endpoint, the RR of ACR20).

The results for the primary efficacy outcome for the Full Analysis Set (ITT population) and the Per-protocol Analysis Set (PP population) are summarised in Tables 14 and 15 respectively. The risk difference is also shown in the tables.

In the Full Analysis Set (ITT population), the RR of ACR20 at Week 24 was 1.039 (90% CI: 0.954, 1.133; 95% CI: 0.938, 1.152).

In the Per-protocol Analysis Set (PP population), the RR of ACR20 at Week 24 was 1.009 (90% CI: 0.927, 1.098; 95% CI: 0.912, 1.115).

Table 14: Study 20120262: Analysis of ACR20 at Week 24 by treatment (Full Analysis Set)

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.

Table 15: Study 20120262: PP sensitivity analysis of ACR20 at Week 24 by treatment (Per Protocol Analysis Set)

Timepoint	ABP 501 (N = 230)	Adalimumab (N = 233)
Week 24		
ACR20 Responder [n/N1 (%)]	176/230 (76.5)	178/233 (76.4)
ACR20 Non-Responder [n/N1 (%)]	54/230 (23.5)	55/233 (23.6)
Risk Ratio of ACR20[a]	1.009	
90% CI for Risk Ratio of ACR20[a]	(0.927, 1.098)	
95% CI for Risk Ratio of ACR20[a]	(0.912, 1.115)	
Risk Difference of ACR20 (%)[a]	0.444	
90% CI for Risk Difference of ACR20 (%)[a]	(-6.012, 6.901)	
95% CI for Risk Difference of ACR20 (%)[a]	(-7.249, 8.138)	

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 ACR20 results from other sensitivity analyses for Week 24 (including: Full Analysis Set using observed values; Full Analysis Set using the LOCF for actual treatment received; analysis based on backward model selection for the Full Analysis Set using the LOCF; repeated-measures analysis using Full Analysis Set with observed values) were reasonably similar to the results of the primary efficacy analysis.

Comment: The sponsor's criterion for establishing equivalence between ABP 501 and adalimumab for patients in moderate to severe RA is for the 90% CI of the primary endpoint from the ITT population to fall within the pre-determined margin of (0.738, 1/0.738). The results fulfil the stated criterion.

The most relevant sensitivity analysis for this equivalence study is the analysis of the primary endpoint in the per-protocol population. This was provided by the sponsor, and even if the margin and the confidence interval proposed by the sponsor were rejected and a more conservative margin of ±15% and the more conservative CI of 95% were chosen, equivalence between ABP 501 and adalimumab for patients in moderate to severe RA would still be supported by the result (RR of ACR20 at Week 24 = 1.009 (95% CI: 0.912, 1.115)).

A potential limitation includes the concomitant use of another immunomodulator (methotrexate) which has likely reduced the difference in treatment effect between groups.

7.2.1.13. Results for other efficacy outcomes

Secondary endpoint values related to ACR20, ACR50, and ACR70

An overview of the secondary endpoint values related to ACR20, ACR50, and ACR70 is shown in Table 16 (risk ratio between treatment groups) and Table 17 (risk difference between treatment groups). In the sensitivity analyses using the per-protocol analysis set, similar results were observed.

The proportion of ACR20 responders were similar between the treatment groups over the study period (measured at Weeks 2, 4, 8, 12, 18, and 24) (shown in Figure 5).

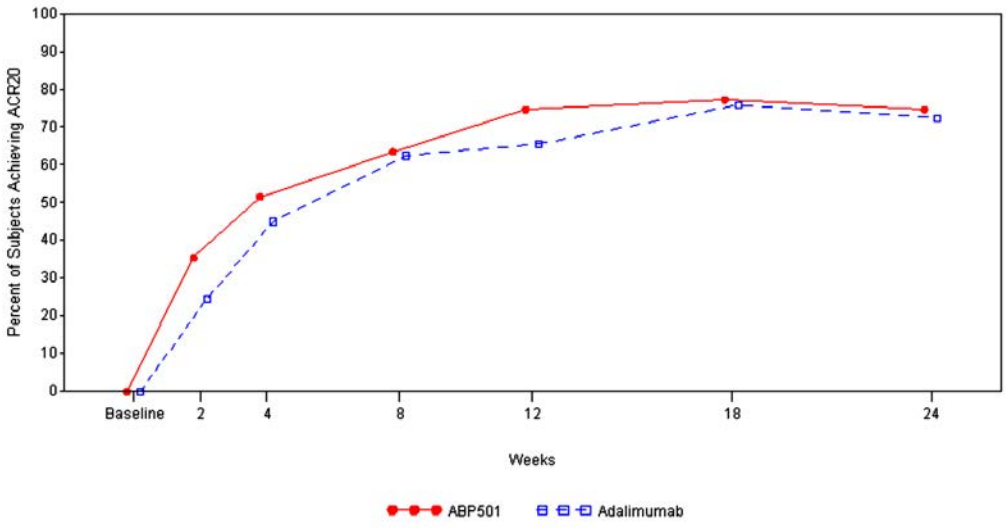
Table 16: Study 20120262 Secondary endpoint values related to ACR20, ACR50, and ACR70; risk ratio between treatment groups (Full Analysis Set)

Score and week	RR of ABP 501 and adalimumab groups	90% CI	95% CI
ACR20 at Week 2	1.421	1.134, 1.781	1.086, 1.860
ACR20 at Week 8	1.015	0.908, 1.134	0.889, 1.158
ACR50 at Week 24	0.948	0.819, 1.097	0.796, 1.128
ACR70 at Week 24	1.130	0.872, 1.464	0.830, 1.538

Table 17: Study 20120262 Secondary endpoint values related to ACR20, ACR50, and ACR70; risk differences between treatment groups (Full Analysis Set)

Score and week	RD between ABP 501 and adalimumab groups	90% CI	95% CI
ACR20 at Week 2	11.038%	4.515%, 17.562%	3.265%, 18.812%
ACR20 at Week 8	0.973%	-5.990%, 7.935%	-7.324%, 9.269%
ACR50 at Week 24	-2.836%	-10.220%, 4.547%	-11.634%, 5.961%
ACR70 at Week 24	3.147%	-3.177%, 9.470%	-4.388%, 10.681%

Figure 5: Study 20120262 Percent of subjects achieving ACR20 by treatment (Full Analysis Set with LOCF)



Secondary endpoint: Change from Baseline of the DAS28-CRP

Disease Activity Score 28-CRP (DAS28-CRP) was measured at Weeks 2, 4, 8, 12, 18, and 24. The mean scores were similar between the treatment groups over the study period. As expected, the mean scores decreased over time in both treatment groups. All the 90% CIs and all 95% CIs were within the pre-defined equivalence margin of (-0.6, 0.6) set by the sponsor. All 90% CIs and all 95% CIs included 0. The mean scores are shown in Table 18.

Table 18: Study 20120262 Difference between treatment groups in the mean change from Baseline in DAS28-CRP (Full Analysis Set)

Week	Mean score difference between ABP 501 and adalimumab groups	90% CI	95% CI
Week 2	-0.05	-0.18, 0.08	-0.20, 0.10
Week 4	-0.02	-0.17, 0.12	-0.20, 0.15
Week 8	-0.08	-0.24, 0.08	-0.27, 0.11
Week 12	-0.09	-0.26, 0.07	-0.29, 0.10
Week 18	-0.09	-0.25, 0.08	-0.29, 0.12
Week 24	-0.01	-0.18, 0.17	-0.22, 0.20

Sensitivity analyses performed for the DAS28-CRP change from baseline (for the Per-protocol Analysis Set and the Full Analysis Set using observed values by actual treatment received) revealed similar results.

Exploratory endpoint: Subject injection site pain perception assessment

The mean injection site pain rating scores were generally lower in the ABP 501 group (mean range: 10.0-10.7 mm) compared to the adalimumab group (mean range: 16.1-21.4 mm) at each study visit. The mean pain scores in the adalimumab group appeared to decrease over the 12 weeks of measurement (from 21.4 mm at baseline to 16.1 mm at Week 12), but never reached the lower levels of the ABP 501 group which remained stable between 10.0 mm and 10.7 mm. The sponsor attributed the difference in pain scores between groups to the use of different excipients in ABP 501. Some result were converted from a 95 mm pain score to a 100 mm pain score, but a sensitivity analysis that excluded the converted scores did not show a significant difference in the results.

Comment: The results of the secondary efficacy endpoints are generally supportive of equivalence. The ACR20 value at Week 12 is considered to be more sensitive to detect potential differences between adalimumab and a biosimilar candidate (Lai and La Noce, 2016). The Week 12 value is not available in the sensitivity analysis, but the Week 8 value supports equivalence as well (RR = 1.015, 95% CI: 0.889, 1.158).

7.2.1.14. Evaluator commentary

Evaluator's comments are provided under each subsection and are not repeated here.

7.3. Indication: Psoriasis

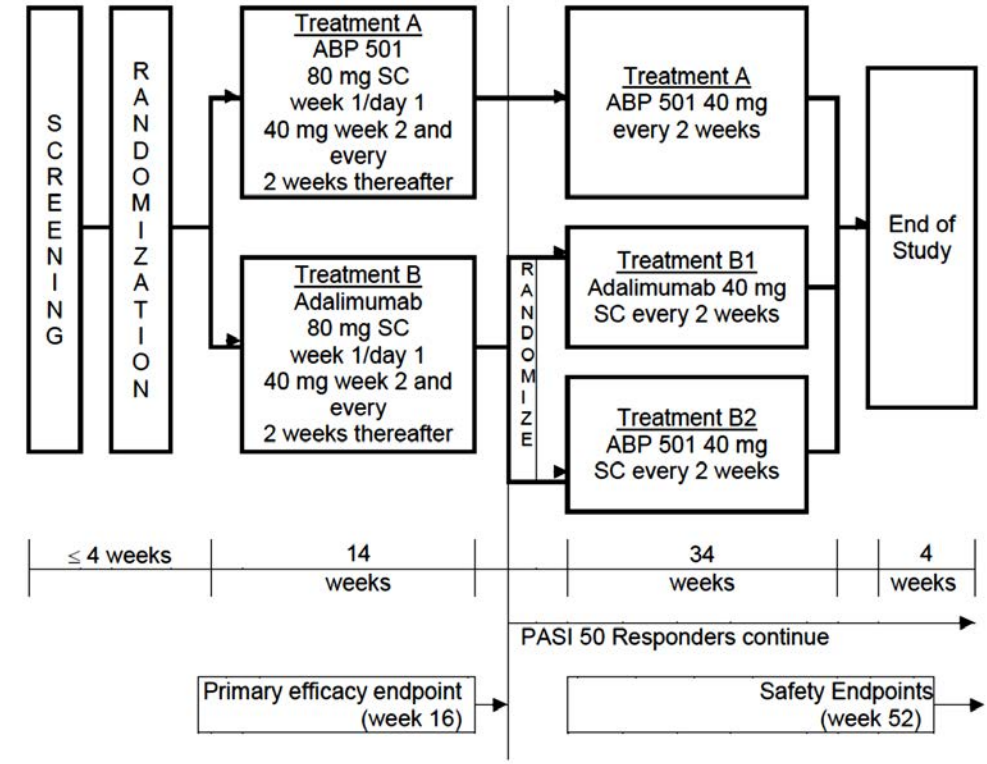
7.3.1. Pivotal or main efficacy study: Study 20120263

7.3.1.1. Study design, objectives, locations and dates

Design

Study 20120263 was a Phase III, double-blind, randomised, active comparator-controlled study in 350 subjects with moderate to severe psoriasis with no concomitant medications allowed for the treatment of psoriasis evaluating the efficacy and safety of ABP 501 compared with adalimumab (EU).

Figure 6. Study 20120263 Study design schema



PASI = Psoriasis Area and Severity Index; SC = subcutaneous

The outline of the study design is shown in Figure 6. The total duration of the study was up to 52 weeks:

- *Screening period (up to 4 weeks):* Subjects were screened and randomised up to 4 weeks before drug administration.
- *Administration period 1 (14 weeks):* Subjects received ABP 501 (Treatment Group A) or adalimumab (Treatment Group B) at an initial loading dose of 80 mg subcutaneous (SC) on Week 1/Day 1, followed by 4 mg SC every other week starting 1 week after the loading dose (that is, Week 2 and every 2 weeks thereafter).
- The primary efficacy endpoint was assessed at Week 16. The subjects that showed a PASI 50 response (50% or better improvement) continued in the study until up to Week 52. Subjects without a PASI 50 response at Week 16 or who missed the week 16 visit were discontinued from the study.
- *Administration period 2 (34 weeks):*
  - Treatment Group A with PASI 50 response at Week 16: continued on the same regimen (ABP 501 40 mg) until Week 48.
  - Treatment Group B with PASI 50 response at Week 16: was re-randomised and then split into 2 groups, namely:
    - Treatment Group B1: continued on adalimumab 40 mg SC until Week 48.
    - Treatment Group B2: switched to ABP 501 40 mg SC until Week 48.
- Final efficacy assessments (Week 50).
- End of study visit (Week 52).

Objectives

Primary study objective: 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 adalimumab.

Secondary study objectives: to assess the safety and immunogenicity of ABP 501 compared with adalimumab 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.

Exploratory objectives: to assess the perception of injection site pain based on subjects' rankings for ABP 501 compared with adalimumab injections.

Location and dates

The study was conducted at 49 centres in 6 countries (Australia, Canada, France, Germany, Hungary, and Poland between 18 October 2013 (first subject enrolled) and 18 March 2015 (last subject completed).

7.3.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- 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 (for example, methotrexate, cyclosporine, psoralen plus ultraviolet light A).
- Subject had no known has no known history of active tuberculosis (including a negative tuberculosis screening test).

The exclusion criteria included:

- Diagnosis of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (for example, eczema).
- Subjects that have previously used: 2 or more biologics for treatment of psoriasis, adalimumab, or a biosimilar of adalimumab.
- Active, recurrent, or chronic infections, history of serious infections (including HIV, HBV, HCV, and TB).
- Uncontrolled clinically significant systemic disease, active neurological disease, NYHA III/IV heart failure, or another potentially interfering disease).
- History of malignancy within 5 years (except cured cutaneous SCC, BCC, in situ cervical cancer, or in situ breast ductal carcinoma).
- Hypersensitivity to any active or excipient.
- Laboratory abnormalities (Hb < 9 g/dL; platelets < 100,000/mm^3; white blood cell count < 3,000 cells/mm^3; AST and ALT > 2 x ULN; creatinine clearance < 50 mL/min (Cockroft-Gault formula); any other potentially interfering abnormality).

- Washouts/non-permitted treatments:
  - Within 14 days prior: UVB therapy; topical psoriasis therapy.
  - Within 28 days prior: UVA therapy or excimer laser; non-biologic systemic therapy for psoriasis (except otic/nasal/inhaled corticosteroids); live vaccines.
  - Within 1 month prior: etanercept.
  - Within 3 months prior: ustekinumab; other anti-TNF agents.
- Other exclusions: substance abuse, pregnancy, breast feeding, absence of adequate contraception, planned surgical procedures, or inability to comply with the study procedures.

Comment: The inclusion and exclusion criteria that were used in the study are acceptable, as they provide a reasonable balance between internal and external validity. The main inclusion criteria in the REVEAL trial (which investigated the use of reference product Humira in psoriasis; described in Menter *et al*. (2008)) were very similar to the main inclusion criteria in Study 20120263.

7.3.1.3. Study treatments

The initial loading dose of ABP 501 and adalimumab was 80 mg SC at week 1/day 1, followed by 40 mg SC at Week 2, and then 40 mg SC every 2 weeks. This dosing schedule matches the recommended dosing of the reference product for the treatment of psoriasis. Subjects discontinuing from study treatment were offered alternative treatment.

Certain concomitant medications were permitted: Bland moisturisers/emollients (without urea or alpha or beta hydroxy acids) were allowed as needed. Class III to VII topical steroids were permitted on the palms, soles, face and intertriginous areas.

Specific medications were prohibited:

- UVA or UV B light therapy (with or without psoralen); class I to II topical steroids or topical anthralin, or any other topical therapy (unless listed as allowed)
- Any therapy for psoriasis (unless listed as allowed); cyclosporine is prohibited
- Live vaccinations while receiving study drug
- Any experimental (biological or non-biological) therapy

Any other treatment (unless explicitly excluded) deemed necessary may have been given at the discretion of the investigator.

Comment: The dosing schedule and rules were appropriate. The choice of comparator was appropriate. The list of prohibited medications is reasonable. Rescue medications were not specifically mentioned in the study protocol or study report. However, cyclosporine, which is commonly used as rescue medication in psoriasis, was specifically prohibited. Class III to VII topical steroids on the palms, soles, face and intertriginous areas had also been permitted in the pivotal trial of the reference product (Menter *et al*., 2008).

7.3.1.4. Efficacy variables and outcomes

PASI score

For the purposes of this study, the PASI score was used a key psoriasis assessment tool. The PASI measures the average redness (erythema), thickness (induration), and scaliness (each graded on a 0 to 4 scale) of psoriasis lesions, weighted by the area of involvement (Fredriksson and Pettersson, 1978; Feldman and Krueger, 2005; Spuls *et al.*, 2010.). This will result in a score from 0 (no disease) to 72 (maximal disease), but that the upper end of the scale is rarely used.

Typically, a PASI score ≤ 10 is considered to be mild disease, and a score of 10 to 20 moderate, and a score > 20 is considered severe. In this study, the assessments for a given subject were made by the same observer whenever possible.

Primary efficacy variable (endpoint)

The primary efficacy endpoint was the PASI percent improvement from baseline at Week 16.

Secondary efficacy variables (endpoints)

The secondary efficacy endpoints were:

- PASI 75 response at Weeks 16, 32, and 50
- PASI percent improvement from Baseline at Weeks 32 and 50
- sPGA responses (0/1) at Weeks 16, 32, and 50
- BSA involvement at Weeks 16, 32, and 50

Exploratory endpoints

The exploratory endpoint was subject's ranking of pain at injection site at baseline, Weeks 4, 8, and 12.

Comment: The relevant EU guidance 'Guideline on the clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr)' specifies that the PASI score alone is not sufficient to evaluate psoriasis severity. There are multiple known issues with the PASI score, including: uncertain clinical significance of a change in PASI score; reduced usefulness beyond a PASI score of 30; overestimation of the surface area affected. However, there are no widely accepted alternatives and the PASI score has been commonly used in the past and allows for comparison with historical trials.

The PASI score is an indicator in psoriasis that had been used in the reference product pivotal trial (Menter et al., 2008) as one of the two primary endpoints. The reference product trial used 'percentage of subjects achieving PASI 75 response at Week 16' rather than 'PASI percent improvement from Baseline at Week 16'). Therefore, the PASI 75 response at Week 16 needs to be specifically considered in this study. This study uses PASI percent improvement from baseline at Week 16. However, PASI 75 response at Weeks 16, 32, and 50 is included in this study as a secondary endpoint. It could be argued that, for an equivalence trial, the use of the continuous variable 'PASI percent improvement' is more suitable to detect smaller differences in treatment effect than the categorical variable 'PASI 75'.

Both the PASI score and another validated score for psoriasis assessment (for example, the PGA score, or the BSA score) should be used to adequately assess efficacy. But given that this equivalence trial does not aim to establish efficacy de novo, but aims to establish equivalence, and given that the results for scores other than PASI have been provided, the chosen endpoints are acceptable for the purpose of this study.

7.3.1.5. Randomisation and blinding methods

Randomisation

Patients were randomly assigned in a 1:1 ratio to receive either ABP 501 or adalimumab. Randomisation was computer-generated prior to the commencement of the study. The scheme was prepared by a statistician not involved in the study in a blinded fashion using an interactive voice and web response system (IXRS).

As per study design, two sets of randomisation occurred: (1) at study commencement; and (2) at Week 16 when subjects from Treatment Group B with a PASI 50 response were re-randomised and then split into 2 groups.

Both initial randomisation and re-randomisation were stratified by geographic region (Eastern Europe, Western Europe, and other) and prior biologic use for psoriasis (with prior biologic use capped at 50% of the study population).

Blinding

The following were blinded until the end of the study period:

- Subjects
- All personnel involved with the conduct and the interpretation of the study (including investigators, study centre personnel, and sponsor staff)

ABP 501 and adalimumab were provided in prefilled, indistinguishable syringes which were dispensed by the IXRS. However, in an emergency, the treatment assignment could have been retrieved through the IXRS.

After the primary analysis, unblinded personnel reviewed the unblinded study data; they were not involved in the study operations between the primary analysis and the final analysis.

Allocation concealment

Allocation concealment was not specifically discussed.

Comment: The randomisation and blinding methods were adequate.

7.3.1.6. Analysis populations

The analysis populations consisted of the following:

- *Full Analysis Set:* consisted of all subjects initially randomised in the study (based on intention to treat principle). This set was used to perform the primary efficacy analysis.
- *Re-randomised Analysis Set*: consisted of all subjects randomised at Week 16 in the study (based on intention to treat principle).
- *Per-protocol Analysis Sets*: subsets of the Full Analysis Set which included subjects who completed the specified treatment period and did not have a protocol violation that would affect evaluation of the primary objective of the study. Two Per-protocol Analysis Sets were created: (1) based on data up to Week 16; (2) based on data post Week 16. These sets were used for sensitivity analyses of the key efficacy endpoints.
- *Safety Analysis Set*: included all randomised subjects who received at least 1 dose of investigational product. In this study, this is a subset of the Full Analysis Set.
- *Antidrug Antibody Analysis Set*: consisted of the subset of subjects in the safety analysis set who had at least one evaluable antibody test result (to either ABP 501 or adalimumab). Immunogenicity data from subjects were analysed according to the actual treatment received.
- *Pharmacokinetic Analysis Set*: consisted of the subset of subjects in the safety analysis set who had at least one evaluable result for serum concentration of ABP 501 or adalimumab (including results below the level of detection). Pharmacokinetic concentration data from subjects were analysed according to the actual treatment received.

Comment: The primary efficacy analysis was conducted using the intention-to-treat (ITT) population (Full Analysis Set) and is the preferred method for superiority trials. There is no overall consensus on whether intention-to-treat population (ITT) or per-protocol (PP) population is preferable for equivalence trials. ITT analyses often

tend to bias the results toward equivalence. The preferred method is to provide analyses of both ITT and PP population sets, and the sponsor has done so at least for the key efficacy endpoints. The main analysis population matched the population specified in the study protocol.

7.3.1.7. Sample size

For the determination of equivalence between ABP 501 and adalimumab treatment groups based on the primary endpoint (PASI percent improvement from baseline at Week 16), a sample size of 340 subjects was chosen based on the following assumptions:

- 1:1 randomisation (ABP 501 : adalimumab) (until Week 16 only)
- Power > 90%
- Equivalence margin of ±15% with a significance level of 0.025.

Furthermore, the determined sample size for the primary endpoint was expected to achieve 80% power to demonstrate non-inferiority at a significance level of 0.025 on Week 52 immunogenicity with a non-inferiority margin of 21.7%, which is one-third of the estimated Week 52 immunogenicity rate of 65%.

Comment: The assumptions used for determining the sample size are reasonable. However, the sponsor should have also considered sample size calculations for at least one of the secondary efficacy endpoints.

7.3.1.8. Statistical methods

Inferential analyses will only be performed for the primary endpoint, and the analyses on the secondary variables are to be considered descriptive. All endpoints had descriptive summaries: categorical variable results were shown using the number and per cent of subjects in each category; the continuous variable results were shown using mean, standard deviation, median, minimum, maximum, and number of subjects with observations.

For the primary analysis (PASI change from baseline at Week 16), the 'Last Observation Carried Forward' method was used to accommodate missing data.

For post Week 16 re-randomisation data, analysis was conducted on the observed data only. Missing efficacy endpoints were not imputed.

For sensitivity analyses of efficacy endpoints, the Full Analysis Set and per-protocol analysis sets also used observed cases (without LOCF). For sensitivity analyses of binary efficacy endpoints, subjects with a missing binary response were imputed as non-responders for the Full Analysis Set.

Primary endpoint

The primary endpoint was the PASI percent improvement from baseline to Week 16. Clinical equivalence of the primary endpoint was evaluated by comparing the 2-sided 95% confidence interval (CI) of using a pre-specified equivalence margin of (-15, 15). The 2-sided 95% CI of the group difference was estimated using an ANCOVA model. Covariates were baseline PASI score and stratification factors (geographic region and prior biologic use for psoriasis).

Secondary endpoints

Secondary efficacy endpoints were: PASI 75 response at Weeks 16, 32, and 50; PASI percent improvement from baseline at Weeks 32 and 50; sPGA responses (0/1) at Weeks 16, 32, and 50; BSA involvement at Weeks 16, 32, and 50.

PASI 75 and PASI 50 response at Weeks 4, 8, 12, and 16: 90% and 95% CIs for the risk difference (RD) and risk ratio (RR) between treatment group A and B were estimated using a generalised linear model with stratification factors and baseline PASI score as covariates.

PASI 75 and PASI 50 response at Weeks 32 and 50: 90% and 95% CIs for the risk difference (RD) and risk ratio (RR) between groups A and B1, and between groups B2 and B1 were estimated using a generalised linear model with stratification factors and baseline PASI score as covariates.

PASI percent improvement from Baseline at Weeks 32 and 50: 90% and 95% CIs for the risk difference (RD) between groups A and B1, and between groups B2 and B1 were estimated using an ANCOVA model that contained all 3 treatment combinations and had baseline PASI score and stratification factors (geographic region and prior biologic use for psoriasis) as covariates.

sPGA responses (0/1) at Weeks 16, 32, and 50: 90% and 95% CIs for the RD and RR of sPGA response were estimated using a generalised linear model (a log-binomial regression model) adjusted for the stratification factors and baseline sPGA categories.

BSA involvement at Weeks 16, 32, and 50: 90% and 95% CIs for the differences in change from baseline:

- between groups A and B (Week 16);
- between groups A and B1, and between groups B2 and B1 (Weeks 32 and 50)

were estimated using an ANCOVA model with baseline BSA score and stratification factors (geographic region and prior biologic use for psoriasis) as covariates.

Primary endpoint equivalence margin

No justification for the primary endpoint equivalence margin was given in the original dossier submitted to the TGA. The sponsor was invited to provide a more detailed justification for the equivalence margin chosen (±15%) which was provided and is incorporated below. The sponsor used a similar methodology as in Study 20120262 (RA study) (described in Section 7.2.1.8).

It is best practice to determine the anticipated treatment effect from historical randomised clinical trials of adalimumab for the treatment of plaque psoriasis, ideally by using results from a meta-analysis of multiple studies. The sponsor identified five relevant studies in a literature review, all of which also used PASI improvement percentage as a variable (Table 19).

Table 19: Study 20120263 PASI improvement results from randomised controlled trials with adalimumab for plaque psoriasis (including meta-analysis of selected trials)

Study	Number of Patients		Results: PASI % Improvement			Study Population
	Adalimumab	Placebo	Week	Adalimumab	Placebo	
Gordon, 2006	45	52	Week 12	70	14	Anti-TNF naïve, low- to mid-potency topical corticosteroids allowed
			Week 16	~74		
Menter, 2008 (REVEAL)	814	398	Week 12	76	15	Low- to mid-potency topical corticosteroids allowed, 11-13% prior biologic use
Saurat, 2008 (CHAMPION)	108	53	Week 16	80.8	21.5	Native to anti-TNF and MTX, low-potency topical corticosteroids and Bland emollients allowed
Thaci, 2010 (BELIEVE)	364	NA	Week 16	NA	NA	Failed or intolerant to ≥2 systemic therapies; subjects randomized to receive either "ADA + topical C/B" or "ADA + drug-free vehicle"
Asahina, 2009	43	46	Week 16	~75	~15	Japanese patients; Anti-TNF-naïve; low- to mid-potency topical corticosteroids
				Mean Difference (80%)		Margin to preserver half of effect
Meta-analysis based on REVEAL + CHAMPION + Asahina 2009 + Gordon, 2006#				60.4 (57.98, 62.82)		±29
Meta-analysis based on REVEAL + CHAMPION + Asahina 2009#				60.74 (58.23, 63.26)		±29
Meta-analysis based on REVEAL + CHAMPION#				60.8 (58.19, 63.41)		±29

A standard deviation of 31.7 was assumed for PASI % improvement in the meta-analysis

Four of those trials (Menter *et al*., 2008 (REVEAL trial); Saurat *et al*., 2006 (CHAMPION trial); Asahina *et al*., 2009; Gordon *et al*., 2006) were used to calculate a pooled treatment effect by meta-analysis. The trial described in Thaci *et al*. (2010) was not considered in the sponsor meta-analysis. The calculated pooled treatment effect was used for the equivalence margin calculations.

The equivalence margin was calculated as follows (methodology as suggested by the FDA draft guidance for industry: Non-Inferiority Clinical Trials (March 2010) (FDA, 2010)):

- The point estimate of the mean difference of PASI percentage improvement between placebo and adalimumab was determined to be 60.4% with an 80% confidence interval of (57.98, 62.82).
- The non-inferiority side of the equivalence margin was calculated using half of the lower 80% confidence bound (57.98%/2 = 28.99% rounded to 29%). Consequently, -29% would be the lower bound of the equivalence margin, and +29% the upper bound (on a linear scale). However, the sponsor reduced the margin further from ±29% to ±15% based on *'clinical judgment'* and *'for additional clinical rigor in showing no clinically meaningful differences'.* No further detail was given with regard to the reduction of the margin size.

Comment: The sponsor's statistical analysis plan is acceptable. With regard to the equivalence margin calculations, the trial described in Thaci *et al*., 2010 was not used in the meta-analysis, presumably as it compared treatment with adalimumab with topical calcipotriol/betamethasone to treatment with adalimumab without those topical agents, and therefore could not provide a treatment difference value between adalimumab and placebo. The methodology for determining the equivalence margin based on the FDA guidance appears reasonable. However, it is unclear what clinical judgment was employed to reduce the margin further, as described above. A reduction in equivalence margin is the more conservative approach and there is no objection to doing so, in particular as the usually accepted maximum margin is ± 15%. More details should be provided on the clinical judgement mentioned and the choice of ± 15% as the margin. This constitutes a process issue rather than an outcome issue.

7.3.1.9. Participant flow

350 subjects (175 subjects in each treatment group) were enrolled and randomised in this study, and 347 of these subjects (99.1%) received at least 1 dose of investigational product.

326 of 350 subjects (93.1%) completed the study at Week 16:

- 164 subjects (93.7%) in Group A (ABP 501)
- 162 subjects (92.6%) in Group B (adalimumab)

308 of originally 350 subjects continued post Week 16. 42 subjects (12.0%) did not continue post Week 16 and the most common reason was protocol-specified criteria (21 subjects (6.0%), for example, failure to reach PASI 50).

Of the 308 subjects continuing post Week 16 (drug up to Week 16/drug post Week 16):

- 152 were in Group A (ABP 501/ABP 501)
- 156 from Group B were re-randomised into:
  - Group B1 (79 subjects) (adalimumab/adalimumab)
  - Group B2 (77 subjects) (adalimumab/ABP 501)

Overall, from baseline to the end of the study, 275 (out of 350 initial subjects (78.6%); out of 308 subjects continuing at Week 16 (89.3%)) completed the study:

- 135 in Group A (ABP 501/ABP 501) (88.8%)
- 71 in Group B1 (adalimumab/adalimumab) (89.9%)
- 69 in Group B2 (adalimumab/ABP 501) (89.6%).

42 subjects discontinued before or at Week 16, and 33 subjects discontinued post Week 16.

The most common reasons for discontinuing the study post-Week 16 were: withdrawn consent; adverse events, lack of efficacy, and noncompliance.

With regard to analysis sets, the data are as follows:

- Full Analysis Set: N = 350

  Consisted of all subjects initially randomised in the study (based on intention to treat principle). This set was used to perform the primary efficacy analysis.

- Per-protocol Analysis Set (based on data up to Week 16): N = 310

  Subsets of the Full Analysis Set which included subjects who completed the specified treatment period and did not have a protocol violation that would affect evaluation of the primary objective of the study.

- Per-protocol Analysis Set (based on data post Week 16): *not reported in the study report.* Re-randomised Analysis Set: N = 308

  Consisted of all subjects that continued from week 16 onwards (with treatment assignment based on intention to treat principle).

- Safety Analysis Set: N = 347

  Included all randomised subjects who received at least 1 dose of investigational product. In this study, this is a subset of the Full Analysis Set.

- Antidrug Antibody Analysis Set: N = 347

  Consisted of the subset of subjects in the safety analysis set who had at least 1 evaluable antibody test result (to either ABP 501 or adalimumab). Immunogenicity data from subjects were analysed according to the actual treatment received.

- Pharmacokinetic Analysis Set: N = 347

  Consisted of the subset of subjects in the safety analysis set who had at least 1 evaluable result for serum concentration of ABP 501 or adalimumab (including results below the level of detection). Pharmacokinetic concentration data from subjects were analysed according to the actual treatment received.

Comment: The Full Analysis Set followed the ITT principle which constituted the primary analysis set. If too many patients are lost to follow up, differences between groups could be reduced and equivalence may be falsely concluded. The sponsor has conducted appropriate sensitivity analyses with the Per-protocol Analysis Set for the key efficacy endpoints up to Week 16. The evaluator was unable to locate the any per-protocol analyses for data beyond Week 16. The sponsor should provide these per-protocol analyses.

7.3.1.10. Major protocol violations/deviations

Baseline to Week 16

35 of 350 subjects (10.0%) had one or more major protocol violations from baseline through to Week 16, and the proportion was reasonably similar in each group (9.7% in the ABP 501 group,

and 10.3% in the adalimumab group). A summary of eligibility related protocol violations is shown in (a subset of those shown in Table 20).

Table 20: Study 20120263:Major protocol violations by initial treatment group; Baseline to Week 16 (Full Analysis Set)

Protocol Violation	Treatment Group A (ABP 501) (N = 175) n (%)	Treatment Group B (Adalimumab) (N = 175) n (%)	Total (N = 350) n (%)
Total	17 (9.7)	18 (10.3)	35 (10.0)
Mis-stratification at randomization	7 (4.0)	6 (3.4)	13 (3.7)
Prohibited medications during study[a]	5 (2.9)	2 (1.1)	7 (2.0)
Missed ADA at baseline or week 20	3 (1.7)	3 (1.7)	6 (1.7)
Prior use of 2 or more biologic therapies	0 (0.0)	4 (2.3)	4 (1.1)
Incorrect treatment received[b]	1 (0.6)	2 (1.1)	3 (0.9)
Did not have previous failure to psoriatic systemic therapy	0 (0.0)	1 (0.6)	1 (0.3)
Informed consent not provided[c]	1 (0.6)	0 (0.0)	1 (0.3)

ADA = antidrug antibody
[a] The most commonly used prohibited medications during this study were topical steroids (Listing 16-2.2).
[b] All 3 subjects received an incorrect investigational product different from the investigational product box number assigned by IXRS (Listing 16-2.2). For 2 of these subjects (1 in Treatment Group A, 1 in Treatment Group B), the incorrect investigational product box number resulted in these subjects receiving the opposite investigational product from which they were randomized to (source available upon request).
[c] Informed consent form was to be completed before screening procedures; however, for Subject 26329002007, a pharmacogenetic sample was collected before the pharmacogenetic informed consent form was signed (Listing 16-2.2)
Note: For each category of protocol violation, subjects are included only once, even if they had multiple violations in the same category.

Table 21: Study 20120263 Eligibility related protocol deviations/violations by initial treatment (Full Analysis Set).

Deviation/Violation	ABP 501 (N = 175) n (%)	Adalimumab (N = 175) n (%)	Total (N = 350) n (%)
Subjects with at least one eligibility related protocol deviation/violation	3 (1.7)	8 (4.6)	11 (3.1)
Prior use of 2 or more biologic therapies	0 (0.0)	4 (2.3)	4 (1.1)
Laboratory abnormalities at screening	2 (1.1)	1 (0.6)	3 (0.9)
Did not have previous failure to psoriatic systemic therapy	0 (0.0)	1 (0.6)	1 (0.3)
History of HIV	0 (0.0)	1 (0.6)	1 (0.3)
Informed consent not provided	1 (0.6)	0 (0.0)	1 (0.3)
Planned surgical intervention	0 (0.0)	1 (0.6)	1 (0.3)
Positive PPD with postive quantiferon, symptoms of TB, or without adequate prophylaxis	0 (0.0)	1 (0.6)	1 (0.3)

Note: For each deviation/violation, subjects are included only once, even if they experienced multiple events in that deviation/violation.

Baseline to end of study

59 of 350 subjects (16.9%) had 1 or more major protocol violations from baseline through to the end of study. The most common major protocol violation was use of prohibited medications during the study and the proportion was reasonably similar in each group. A summary of major protocol violations is shown in Table 22.

Table 22: Study 20120263 Major protocol violations by initial/re-randomised treatment group; baseline to end of study (Full Analysis Set)

	Non Re-randomized		Re-randomized			
Protocol Violation	Treatment A (ABP 501) (N = 23) n (%)	Treatment B (Adalimumab) (N = 19) n (%)	Treatment A (ABP 501/ ABP 501) (N = 152) n (%)	Treatment B1 (Adalimumab/ Adalimumab) (N = 79) n (%)	Treatment B2 (Adalimumab/ ABP 501) (N = 77) N (%)	Total (N = 350) n (%)
Total	5 (21.7)	3 (15.8)	24 (15.8)	14 (17.7)	13 (16.9)	59 (16.9)
Prohibited medications during study[a]	3 (13.0)	1 (5.3)	9 (5.9)	3 (3.8)	6 (7.8)	22 (6.3)
Mis-stratification at randomization	1 (4.3)	0 (0.0)	6 (3.9)	4 (5.1)	2 (2.6)	13 (3.7)
Missed ADA at baseline or week 20	0 (0.0)	0 (0.0)	4 (2.6)	3 (3.8)	2 (2.6)	9 (2.6)
Incorrect treatment received[b]	0 (0.0)	0 (0.0)	5 (3.3)	2 (2.5)	1 (1.3)	8 (2.3)
Prior use of 2 or more biologic therapies	0 (0.0)	2 (10.5)	0 (0.0)	0 (0.0)	2 (2.6)	4 (1.1)
Dosed with compromised IP[c]	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	0 (0.0)	2 (0.6)
Did not have previous failure to psoriatic systemic therapy	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.3)
Informed consent not provided[d]	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

ADA = antidrug antibody; IP = investigational product
[a] The most commonly used prohibited medications during this study were topical steroids (Listing 16-2.2).
[b] All subjects received an incorrect investigational product different from the investigational product box number assigned by IXRS, with the exception of 2 subjects (1 in Treatment Group A [ABP 501/ABP 501], 1 in Treatment Group B1 [adalimumab/adalimumab]) who received 2 doses of investigational product at week 16 (Listing 16-2.2). Among the 6 subjects who received an incorrect investigational box number, for 3 subjects (2 in Treatment Group A [ABP 501/ABP 501], 1 in Treatment Group B1 [adalimumab/adalimumab]), the incorrect investigational product number resulted in these subjects receiving the opposite investigational product from which they were randomized or re-randomized to (source available upon request).
[c] The week 36 and 38 investigational product doses received by Subjects 26326001002 and 26326001003 were determined to have been damaged by a temperature excursion (Listing 16-2.2).
[d] Informed consent form was to be completed before screening procedures; however, for Subject 26329002007, a pharmacogenetic sample was collected before the pharmacogenetic informed consent form was signed (Listing 16-2.2)
Note: For each category and violation, subjects are included only once, even if they had multiple violations in the same category.

Comment: The protocol violation/deviation proportions were reasonably similar in both treatment groups up to Week 16, and also reasonably similar in the three treatment groups beyond week 16.

To mitigate the potential effect of protocol violations/deviations, the sponsor has conducted appropriate sensitivity analyses with the Per-protocol Analysis Set (which excluded subjects for whom major violations were recorded) for subjects up to Week 16. However, as stated above, there appears to be no Per-protocol Analysis Set for the study period beyond Week 16.

7.3.1.11. Baseline data

Both the demographic and the psoriasis-related baseline characteristic proportions were reasonably balanced between treatment groups (ABP 501 and adalimumab) in the Full Analysis Set, the Re-randomised Analysis Set, and the per-protocol analysis set.

The following proportions refer to the Full Analysis Set.

The overall mean age was 44.6 years (range 18 to 74 years). The majority of subjects were male (65.1%, 228/350). The majority of subjects were Caucasian (92.6%, 324/350). The duration of psoriasis refers to the time since diagnosis. 91.7% of subjects had psoriasis duration of ≥ 5 years (92.0% (ABP 501) and 91.4% (adalimumab). The mean duration was 20.09 years and the median duration was 18.00 years.

The mean PASI score was 20.08 (a PASI score > 20 is considered severe disease) and the median score was 17.50 (range 12.0 to 61.8) (a PASI score of 10-20 is considered moderate disease). The mean BSA affected by psoriasis was 26.9% and the median score was 21.0% (range 10 to 90%). With regard to sPGA scores (clear, almost clear, mild, moderate, severe, very severe), the number of subjects were: 208 (moderate), 122 (severe), and 17 (very severe). No subjects were in the sPGA category of clear, almost clear, or mild.

82.0% of subjects (287/350) had prior biological agent use for psoriasis, 75.1% (263/350) had prior use of systemic or phototherapies, but only 10.3% (36/350) had been using concomitant topical steroids. The summarised baseline medication status for psoriasis was reasonably balanced between treatment groups.

Baseline data post-Week 16

The baseline demographic data were similar when comparing the total population at baseline and the group that reached PASI 50 and progressed past Week 16.

Comment: The Full Analysis Set which was the set used for the primary analysis by the sponsor was reasonably balanced between treatment groups. The Per-protocol Analysis Set up to Week 16 was also reasonably balanced between treatment groups. The characteristics shown reflect the population of patients with moderate to severe psoriasis reasonably well (for example, when comparing the study population to the population described in Daudén *et al*. (2013), which assessed the characteristics of 1217 patients with moderate to severe psoriasis in 123 centres in Spain, even though the Spanish study had more patients with milder psoriasis) which is supporting the external validity of the study. The demographics were even more similar to the pivotal adalimumab trial (Menter *et al*., 2008) than to the population described in Daudén *et al*. (2013). The psoriasis scoring systems appear to be more subjective than the RA scoring systems, and less likely to be useful on their own, but generally accepted in psoriasis trials when used in combination with another validated psoriasis score. These scoring systems have been used for approved biological therapies for treatment of psoriasis for example, infliximab. In summary, the baseline data is sufficiently balanced between treatment groups and sufficiently similar to the pivotal adalimumab trial for psoriasis to support internal validity and sufficiently similar to a real-world moderate to severe psoriasis population to support external validity.

7.3.1.12. Results for the primary efficacy outcome

The primary efficacy endpoint was the PASI percent improvement from baseline at Week 16. The Full Analysis Set was used for this endpoint. The Per-protocol Analysis Set was also used for a sensitivity analysis. However, no per-protocol analysis data was available for the time period beyond Week 16.

The results for the primary efficacy outcome are for the Full Analysis Set (ITT population; with LOCF), the Full Analysis Set (ITT population; with observed data), and the Per-protocol Analysis Set (PP population; with observed data) are summarised in Tables 23 to 25.

In the Full Analysis Set (ITT population; with LOCF), the PASI Percent Improvement from Baseline at Week 16 was 80.91% in Treatment Group A (ABP 501) and 83.06% in Treatment Group B (adalimumab). The least-squares mean difference between the 2 treatment groups was: -2.18% (90% CI: -6.55%, 2.18%; 95% CI: -7.39%, 3.02%) (Table 23).

In the Full Analysis Set (ITT population; with observed data), the PASI Percent Improvement from Baseline at Week 16 was 80.91% in Treatment Group A (ABP 501) and 83.06% in Treatment Group B (adalimumab). The least-squares mean difference between the 2 treatment groups was: -2.18% (90% CI: -6.55%, 2.18%; 95% CI: -7.39%, 3.02%) (Table 24).

In the Per-protocol Analysis Set (PP population; with observed data), the PASI Percent Improvement from Baseline at Week 16 was 82.62% in Treatment Group A (ABP 501) and 85.34% in Treatment Group B (adalimumab). The least-squares mean difference between the 2 treatment groups was: -2.64% (90% CI: -6.20%, 0.91%; 95% CI: -6.89%, 1.60%) (Table 25).

In the primary analysis, as well as the two main sensitivity analyses, the 95% CI was within the pre-specified equivalence margin.

Table 23: Study 20120263 Summary of PASI percent improvement from Baseline to Week 16 (Full Analysis Set, LOCF)

	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.
Source: Table 14-4.1.1 and Table 14-4.1.4

Table 24: Study 20120263: Summary of PASI percent improvement from Baseline to Week 16 (Full Analysis Set, as observed)

	ABP 501 (N = 175)		Adalimumab (N = 175)	
Timepoint	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Week 16				
n	165	165	167	167
Mean (std)	3.44 (4.705)	82.57 (20.598)	3.12 (5.709)	84.06 (24.218)
Median	1.60	89.87	2.00	89.90
Q1, Q3	0.60, 4.20	76.14, 97.22	0.60, 3.20	81.25, 97.46
Min, Max	0.0, 28.8	9.0, 100.0	0.0, 59.0	-128.7, 100.0
Treatment Difference[a]		-1.46		
95% CI for Difference[a]		(-6.31, 3.39)		
90% CI for Difference[a]		(-5.53, 2.61)		

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

Table 25: Study 20120263: Summary of PASI percent improvement from Baseline to Week 16 (Per Protocol Analysis Set for Week 16, as observed)

	ABP 501 (N = 157)		Adalimumab (N = 153)	
Timepoint	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Week 16				
n	155	155	152	152
Mean (std)	3.36 (4.516)	82.62 (20.068)	2.83 (3.785)	85.34 (17.474)
Median	1.60	89.77	2.00	89.97
Q1, Q3	0.40, 4.20	76.00, 97.22	0.60, 3.20	81.25, 97.42
Min, Max	0.0, 28.8	13.3, 100.0	0.0, 30.8	0.0, 100.0
Treatment Difference[a]		-2.64		
95% CI for Difference[a]		(-6.89, 1.60)		
90% CI for Difference[a]		(-6.20, 0.91)		

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

The remaining two sensitivity analyses (one based on repeated measures and the other using a backward model selection with the final model adjusting for neutralising antidrug antibody status, sex, and prior use of systemic therapies or phototherapies) revealed results the 95%CI of which were also within the pre-determined margin (-1.45% (95% CI -6.33%, 3.43%) and -3.46% (95% CI -8.22%, 1.29%) respectively).

Subgroup analyses included differences in PASI percent improvement 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; neutralising antidrug antibody status. The subgroup results were similar to the entire group result. Confidence intervals were wider where the subgroups were small and not sufficiently powered. However, in both female and male subgroups the criteria for equivalence were met in each group independently at Week 16.

Comment: The sponsor's criterion for establishing equivalence between ABP 501 and adalimumab for patients in moderate to severe psoriasis is for the 95% CI of the primary endpoint from the ITT population (with LOCF) to fall within the pre-determined margin of (± 15%). The results fulfil the stated criterion. The most relevant sensitivity analysis for this equivalence study is the analysis of the primary endpoint in the per-protocol population. This was provided by the sponsor, and equivalence between ABP 501 and adalimumab for patients in moderate to severe psoriasis is supported by the result (The least-squares mean difference between the two treatment groups was: -2.64% (95% CI: -6.89, 1.60)).

7.3.1.13. Results for other efficacy outcomes

The secondary efficacy endpoints were:

- PASI 75 response at Weeks 16, 32, and 50
- PASI percent improvement from baseline at Weeks 32 and 50
- sPGA responses (0/1) at Weeks 16, 32, and 50
- BSA involvement at Weeks 16, 32, and 50

The Week 16 analysis used the assessed differences between:

- Treatment Group A (ABP 501) and Treatment Group B (adalimumab).

The Week 32 and 50 analyses assessed differences between:

- Treatment Group A (ABP 501/ABP 501) and Treatment Group B1 (adalimumab/adalimumab); and
- Treatment Group B2 (adalimumab/ABP 501) and Treatment Group B1 (adalimumab/adalimumab).

The treatment differences were estimated using an ANCOVA model adjusted for the following factors: prior biologic use for PsO, region and baseline scores/categories.

Baseline demographics at Week 16

The baseline demographic data were similar when comparing the total population at baseline and the group that reached PASI 50 and progressed past Week 16. An excerpt from another table that shows the mean and median PASI scores in each group is reproduced below (Table 26).

Table 26: Study 20120263: PASI score baseline characteristics by initial/re-randomised treatment (Full Analysis Set)

Variable	Non Re-randomized		Re-randomized			
	ABP 501 (N = 23) n (%)	Adalimumab (N = 19) n (%)	ABP 501/ ABP 501 (N = 152) n (%)	Adalimumab/ Adalimumab (N = 79) n (%)	Adalimumab/ ABP 501 (N = 77) n (%)	Total (N = 350) n (%)
PASI Score						
n	22	17	152	79	77	347
Mean (std)	20.47 (8.445)	18.59 (7.192)	19.57 (8.071)	20.91 (8.366)	20.46 (7.538)	20.08 (7.990)
Median	19.55	16.40	16.85	18.50	18.80	17.50
Q1, Q3	14.20, 24.00	14.00, 20.40	13.80, 21.90	14.70, 24.90	14.70, 25.50	14.10, 24.00
Min, Max	12.0, 43.9	12.3, 40.4	12.0, 61.8	12.0, 47.7	12.0, 52.2	12.0, 61.8

PASI 75 response at Week 16

Based on the full analysis set (LOCF):

- *Week 16:* The PASI 75 response proportions were 74.4% (ABP 501) and 82.7% (adalimumab). The treatment difference between Group A and Group B was -7.729% with a 95% CI of (-16.620%, 1.163%).

Based on the per-protocol analysis set (observed cases):

- *Week 16:* The PASI 75 response proportions were 76.1% (ABP 501) and 83.6% (adalimumab). The treatment difference between Group A and Group B was -6.983% with a 95% CI of (-15.888%, 1.922%).

sPGA positive responses (0/1) at Week 16

Based on the full analysis set (LOCF):

- *Week 16:* The mean sPGA responses were 58.7% (ABP 501) and 65.3% (adalimumab). The treatment difference between Group A and Group B was -7.365% with a 95% CI of (-17.203%, 2.472%).

Based on the per-protocol analysis set (observed cases):

- *Week 16:* The mean sPGA responses were 61.3% (ABP 501) and 67.8% (adalimumab). The treatment difference between Group A and Group B was -6.516% with a 95% CI of (-16.887%, 3.855%).

BSA involvement at Week 16 (mean change from Baseline)

Based on the full analysis set (LOCF):

- *Week 16:* The mean BSA changes were -18.0% (ABP 501) and -22.1% (adalimumab). The treatment difference between Group A and Group B was 1.93% with a 95% CI of (-0.24%, 4.10%).

Based on the per-protocol analysis set (observed cases):

- *Week 16:* The mean BSA changes were -18.1% (ABP 501) and -22.7% (adalimumab). The treatment difference between Group A and Group B was 2.13% with a 95% CI of (0.27%, 4.00%).

Results post-Week 16 (PASI 50 responders)

PASI percent improvement from baseline at Weeks 32 and 50

Based on the re-randomised analysis set (observed cases):

- *Week 32:* The mean PASI scores were 2.62 (87.62% mean improvement) (ABP 501/ABP 501), 2.27 (88.16%) (adalimumab/adalimumab), and *2.53 (86.98%)* (adalimumab/ABP

501). The treatment difference between Group A and Group B1 was -0.49% with a 95% CI of (-5.60%, 4.61%). The treatment difference between Group B2 and Group B1 was -1.05 with a 95% CI of (-6.93, 4.84).

- *Week 50:* The mean PASI scores were 2.57 (87.16% mean improvement) (ABP 501/ABP 501), 2.36 (88.11%) (adalimumab/adalimumab), and *2.98 (85.82%)* (adalimumab/ABP 501). The treatment difference between Group A and Group B1 was -1.16 with a 95% CI of (-7.17, 4.86). The treatment difference between Group B2 and Group B1 was -2.37 with a 95% CI of (-9.26, 4.52).

PASI 75 response at Weeks 32 and 50

Based on the re-randomised analysis set (observed cases):

- *Week 32:* The PASI 75 response proportions were 82.5% (ABP 501/ABP 501), 84.7% (adalimumab/adalimumab), and *84.5%* (adalimumab/ABP 501). The treatment difference between Group A and Group B1 was -2.751% with a 95% CI of (-13.935%, 8.433%). The treatment difference between Group B2 and Group B1 was 0.582% with a 95% CI of (-12.899%, 14.063%).
- *Week 50:* The PASI 75 response proportions were 85.1% (ABP 501/ABP 501), 87.1% (adalimumab/adalimumab), and *81.2%* (adalimumab/ABP 501). The treatment difference between Group A and Group B1 was -4.680% with a 95% CI of (-15.263%, 5.904%). The treatment difference between Group B2 and Group B1 was -6.511% with a 95% CI of (-19.058%, 6.037%).

sPGA positive responses (0/1) at Weeks 32 and 50

Based on the re-randomised analysis set (observed cases):

- *Week 32:* The mean sPGA responses were 66.4% (ABP 501/ABP 501), 72.2% (adalimumab/adalimumab), and *70.4%* (adalimumab/ABP 501). The treatment difference between Group A and Group B1 was -8.158% with a 95% CI of (-20.487%, 4.171%). The treatment difference between Group B2 and Group B1 was -4.195% with a 95% CI of (-18.099%, 9.709%).
- *Week 50:* The mean sPGA responses were 68.7% (ABP 501/ABP 501), 74.3% (adalimumab/adalimumab), and 69.6% (adalimumab/ABP 501). The treatment difference between Group A and Group B1 was -9.636% with a 95% CI of (-22.328%, 3.056%). The treatment difference between Group B2 and Group B1 was -7.541% with a 95% CI of (-21.821%, 6.738%).

BSA involvement at Weeks 32 and 50 (mean change from baseline)

Based on the re-randomised analysis set (observed cases):

- *Week 32:* The mean BSA changes were -20.6% (ABP 501/ABP 501), -25.3% (adalimumab/adalimumab), and *-23.8%* (adalimumab/ABP 501). The treatment difference between Group A and Group B1 was 1.51% with a 95% CI of (-0.44%, 3.46%). The treatment difference between Group B2 and Group B1 was 0.83% with a 95% CI of (-1.41%, 3.07%).
- *Week 50:* The mean BSA changes were -20.7% (ABP 501/ABP 501), -25.5% (adalimumab/adalimumab), and *-25.1%* (adalimumab/ABP 501). The treatment difference between Group A and Group B1 was 0.99% with a 95% CI of (-0.91%, 2.90%). The treatment difference between Group B2 and Group B1 was 0.63% with a 95% CI of (-1.55%, 2.81%).

Exploratory endpoints

The exploratory endpoint was subject's ranking of pain at injection site at Baseline, Weeks 4, 8, and 12.

The mean injection site pain rating scores were generally lower in the ABP 501 group (range: 3.3 to 4.5 mm) compared to the adalimumab group (range: 12.4 to 19.3 mm) at each study visit. The mean pain scores decreased over the 12 weeks of measurement (from 4.5 mm at baseline to 3.3 mm at week 12 in the ABP 501 group, and from 19.3 mm at baseline to 12.4 mm at week 12 in the adalimumab group). The sponsor attributed the difference in pain scores between groups to the use of different excipients in ABP 501.

Comment: The results of the secondary efficacy endpoints are generally supportive of equivalence and efficacy throughout the study.

When comparing the secondary endpoint results, the treatment effect appears to be slightly lower in the ABP 501/ABP 501 group. As alluded above, the scoring systems used in psoriasis have a greater degree of subjectivity relative to scoring systems in different diseases (for example, rheumatoid arthritis, which can also be scored with radiographic evidence and biomarkers). With regard to the PASI 75 percentage at Week 16, which was one of the primary endpoints in the REVEAL trial (Menter et al., 2008), the percentage of patients reaching PASI 75 at Week 16 was higher in this study in both groups (74.4% (ABP 501) and 82.7% (adalimumab) compared to 71% (adalimumab in the REVEAL trial) and 7% (placebo in the REVEAL trial)). At Week 32, the PASI 75 proportion had increased further in all groups. But when comparing the secondary endpoint results in Week 32 with Week 50, the scores were generally better in Week 50 in groups A and B1, but slightly worse for group B2 (the adalimumab/ABP 501 single-switch group) for all variables (including PASI 75 proportion) except BSA. This is not necessarily significant, as the study population that switched only consisted of 77 subjects. But a reduction in efficacy may be related to immunogenicity associated with switching and should be further investigated in a post-market setting. Of the 308 subjects in the Re-randomised Analysis Set, 275 subjects (89.3%) completed the study. There appears to be no Per-protocol Analysis Set for the study period beyond week 16 which should be supplied by the sponsor.

7.3.1.14. Evaluator commentary

Evaluator's comments are provided under each subsection (where applicable) and are not repeated here.

7.4. Justification for extrapolation to other indications approved for the reference product

The sponsor has provided a 145-page document which outlines the sponsor's scientific justification for extrapolation of indications. It was not specifically prepared for Australia, that is, contains reference to the indication of hidradenitis suppurativa. At the time of submission, hidradenitis suppurativa was not a registered indication in the reference product Humira in Australia.

The following summarises the sponsor's justification:

7.4.1. Analytical similarities and mechanism of action

- The ABP 501 quality program demonstrated similarity with minimal analytical differences between ABP 501, adalimumab (US), and adalimumab (EU), with no clinically significant functional differences.

- Functional similarity was demonstrated in multiple cell types, including similarity in the potency of inhibition of chemokine production, inhibition of apoptosis and necrosis, binding to TNF-α, and sTNF-α-driven signalling.
- Similarity was shown with regard to antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities, binding to mbTNF-α and for the ability to block proliferation in a mixed lymphocyte reaction (MLR). This may be important for IBD indications.

7.4.2. PK similarities

- Pharmacokinetic similarity of ABP 501 to adalimumab was shown in healthy subjects. Trough PK levels evaluated in the two clinical efficacy studies were also similar between treatment groups. Of the covariates investigated for impact in PK, only the presence of ADAs was clinically significant.

7.4.3. Efficacy similarities

- Studies 20120262 (RA patients with concomitant immunosuppressive therapy) and 20120263 (psoriasis patients; younger with fewer co-morbidities) covered a wide range of individuals and demonstrated clinical equivalence. Given that the efficacy of ABP 501 and adalimumab was found to be similar in the respective studies conducted in RA and Ps, similar achievement of efficacy for ABP 501 and adalimumab would also be expected in other indications for which licensure is sought.
- In Study 20120262, the primary efficacy endpoint, 20% improvement in American College of Rheumatology (ACR) core set measurements (ACR20) at Week 24, was selected for its sensitive nature and durability, and its history of use in all regulatory assessments for approval of adalimumab.
- Study 20120263 in subjects with moderate to severe Ps is considered appropriate to demonstrate similar efficacy of ABP 501 to that of adalimumab based on the large treatment effect and the sensitivity of the clinical assessment of PASI endpoints. Additionally, the Ps patient population tends to be young with few comorbidities and without concomitant immunosuppressive therapy. Thus, it is considered to be sensitive for the purpose of demonstrating no clinically meaningful differences between products.

7.4.4. Dosing considerations

- The dosing regimens across the adult indications in arthritides are identical and adalimumab may be administered as monotherapy or with concomitant medications.
- The clinical efficacy study in psoriasis patients used a similar dosing regimen (80 mg loading dose) to the regimen in Crohn's disease (CD), ulcerative colitis (UC), and HS.

7.4.5. Safety similarities

- There were no clinically meaningful differences in toxicities between treatment groups in either of the clinical efficacy studies. The size of the safety database and the duration of exposure from the 2 clinical studies in therapeutic indications are adequate to inform the toxicities associated with ABP 501 for all indications of use.
- The adverse events of interest from both clinical efficacy studies were similar to the adverse events described published literature for adalimumab.
- In summary, the safety profiles of ABP 501 and adalimumab were found to be similar in the respective studies in the RA and Ps populations as well as in healthy subjects, and are further expected to be similar in all proposed indications of use for which licensure is sought.

7.4.6. Immunogenicity

- The rate of ADA development against adalimumab was generally similar across conditions of use, taking into consideration concomitant MTX use, when compared using the same method. The 2 clinical studies provided a population (RA) with concomitant immunosuppressant therapy (MTX) and a population without concomitant immunosuppressant therapy (Ps). The incidence of developing binding and neutralizing ADAs was similar between the ABP 501 and adalimumab arms in the respective studies. No meaningful differences in the incidence of developing binding and neutralizing ADAs between subjects who underwent a single transition from adalimumab to ABP 501 in Study 20120263, and those who remained on their initial randomised treatment, demonstrates that a single transition from adalimumab to ABP 501 does not pose an increased immunogenicity risk.

7.4.7. Summary

- In summary, the ABP 501 studies in subjects with RA or Ps included sensitive and appropriate populations for the demonstration of similarity in efficacy. Also, the clinical endpoints and the timing of the assessment of those endpoints were appropriate to detect clinically meaningful differences between ABP 501 and adalimumab if such differences exist. No clinically meaningful differences in efficacy were demonstrated between ABP 501 and adalimumab in either study in therapeutic indications. Therefore, these studies provide supporting evidence regarding efficacy to justify extrapolation across all indications of use.

Comment: The sponsor has chosen two appropriate clinical study populations (indications) to enable extrapolation to the other approved indications of the reference product. For extrapolation purposes, the factors to be considered for choosing appropriate indications to investigate the biosimilar candidate include:

- The expected/historical placebo-adjusted response rate in a particular indication under investigation
- A valid clinical model for this class of drug
- An identical (or at least highly similar) dosing regimen
- An identical (or at least highly similar) mechanism of action
- A population that is sufficiently sensitive to immunogenicity
- Generalisability (external validity) of the study sample with regard to relevant populations (including paediatric populations).

The highest placebo-adjusted response rate (that is, the best signal-to noise ratio) should be used to detect differences between treatments (Lee, 2014). Even though the rheumatoid arthritis population appears to be the main population for adalimumab, its signal-to noise ratio is inferior to the relatively high ratio in a psoriasis study population. Despite its potentially lower signal-to noise ratio and concomitant immunomodulator (methotrexate) administration, the RA study is still considered a valid model for testing TNF-α antagonists and sufficiently robust and relevant to patients with other arthritides. The psoriasis study provided a better signal-to noise ratio and also a population more sensitive to immunogenicity making it better for extrapolation, and especially to extrapolation to IBD in that regard.

The dosing regimen is very similar for all approved reference product adult indications. However, no paediatric population was investigated. Malignancies (in particular lymphoma) have been associated with children and adolescents treated

with TNF-α antagonists, including adalimumab. This is currently outlined in the reference product information.

Other areas of TGA may provide advice on similarity of potentially relevant functions in vitro (in particular in vitro comparison of receptor binding). The IBD indications may differ with regard to mechanism of action: the arthritis and psoriasis indications use the Fab region, whereas the Fc region may have a greater role in the IBD indications.

In summary, consideration of each of the studies on their own would have made it difficult to support extrapolation to all other indications. Overall, taking into account the two clinical equivalence studies and the PK study, extrapolation to all currently approved indications of the reference product is supported from a clinical evaluation point of view. However, safety concerns remain that require appropriate monitoring in the post-authorisation phase (especially regarding immunogenicity (in particular in IBD), and paediatric indications).

7.5. Other efficacy studies

Not applicable.

7.6. Analyses performed across trials: pooled and meta analyses

Not applicable.

7.7. Evaluator's conclusions on clinical efficacy

There is sufficient evidence to support clinical efficacy of ABP 501 in rheumatoid arthritis and psoriasis and also biosimilarity of ABP 501 to the reference product adalimumab (Humira).

The sponsor has not nominated one of the provided clinical equivalence studies as the pivotal or main study.

Study 20120262 (RA patients) was the shorter study (26 weeks), but rheumatoid arthritis is arguably the more significant indication for adalimumab. Furthermore, the study population was larger (N = 526, compared to N=350 in the psoriasis study) and older with more co-morbidities. Most other trials of TNF-α antagonist biosimilars used rheumatoid arthritis as their main study indication (Lai and La Noce, 2016).

The investigation of medicines for rheumatoid arthritis has a better choice of endpoints: the ACR score, for example, is highly validated and is also a composite endpoint. Additionally, biomarkers and radiographic evidence can be used for rheumatoid arthritis. The RA study used a highly validated ACR endpoint.

The main limitations of the provided RA study are the shorter study period (that is, no longer term data up to 52 weeks), the wider pre-determined equivalence margin (0.738, 1/0.738), and the concomitant immunomodulator (methotrexate) administration at variable (but stable) doses. Methotrexate had the potential to reduce the occurrence of immunogenicity and to mask the difference in treatment effect between groups. However, the study has an open-label extension up to 72 weeks which should be followed up as a post-authorisation efficacy study. Furthermore, even though the equivalence margin was wider, the main study results (using 95% CI) were also met when the recommended margin of ±15% was applied.

Study 20120263 (psoriasis patients) was the longer study (48 weeks with follow-up until 52 weeks), but had fewer participants compared to the RA study. Psoriasis patients are younger with fewer co-morbidities when compared to RA patients. Even though the psoriasis study had

a longer duration, the primary endpoint was set at Week 16 compared to Week 24 in the RA study. No per-protocol analysis results were supplied for the study period post Week 16.

The psoriasis assessment tools are often considered a limitation of clinical trials in psoriasis patients. Psoriasis assessments appear to be more subjective with clinicians often overestimating body surface area affected. The patient experience of severity is also rather subjective.

The PASI is still considered the gold standard and widely used in psoriasis clinical trials, including the reference product pivotal REVEAL trial. The PASI's disadvantages are that the upper end of the scale is rarely used (the highest score in Study 20120263 was 61.8/72), and may have low response distribution and no consensus on interpretability, whereas sPGA may not necessarily discriminate small change and may not have a robust range (Feldman & Kruger, 2005; Spuls *et al*., 2010). In the relevant EU guideline (CHMP/EWP/2454/02 corr), a combination of endpoint measures is recommended (for example, PASI and sPGA or PASI and BSA) which was used in Study 20120263.

As both supplied clinical studies had strengths and limitations in different areas, they complement each other rather well. Therefore both were used for evaluating efficacy in the tested indication, for establishing equivalence with the reference product, and for extrapolation to the other indications of the reference product. In the evaluator's opinion both were needed to establish the biosimilar status in ABP 501.

As outlined above, based on the evidence available, the approval of extrapolation to the other reference product indications is considered reasonable in conjunction with appropriate pharmacovigilance activities (for example, participation in relevant disease registries) and risk minimisation activities.

8. Clinical safety

8.1. Studies providing evaluable safety data

All three studies (one PK bioequivalence study and two equivalence studies in RA and psoriasis respectively; all described in this report) included in this submission provided safety data:

- Study 20110217: a Phase I, 3 arm parallel group, randomised, single blind, single dose PK similarity study that compared ABP 501 to adalimumab (US) and adalimumab (EU) in 203 healthy men and women (one dose only).
- Study 20120262: a Phase III, double blind, randomised, active comparator-controlled study in 526 subjects with moderate to severe rheumatoid arthritis with concomitant methotrexate and oral corticosteroid use evaluating the efficacy and safety of ABP 501 compared with adalimumab (US) (up to 26 weeks).
- Study 20120263: a Phase III, double blind, randomised, active comparator controlled study in 350 subjects with moderate to severe psoriasis with no concomitant medications allowed for the treatment of psoriasis evaluating the efficacy and safety of ABP 501 compared with adalimumab (EU) (up to 52 weeks).

A summary of the studies providing safety data is in Table 27. Studies 20130258 and 20120176 were ongoing at the data lock point date and not part of this submission.

Table 27: Overview of studies providing evaluable safety data

Type of Study	Study Identifier Protocol No.	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	No. Subjects Enrolled/ Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Duration of Study[a]	Study Status; Type of Report/ Location
Study Reports of Healthy Subject PK and Initial Tolerability								
PK 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	203/203	Healthy male and female subjects, age 18 to 45 yrs BMI 18 to 30 kg/m^2	63 days	Complete, full CSR/ Module 5.3.3.1 (20110217)
Study Reports of Controlled Clinical Studies Pertinent to Claimed Indication								
Efficacy and Safety	20120262	Efficacy, safety, immunogenicity	Phase 3 randomized, double-blind, active comparator-controlled	ABP 501 vs adalimumab (US), 40 mg SC, every other wk	526/526	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, full CSR/ Module 5.3.5.1 (20120262)

Table 27 continued: Overview of studies providing evaluable safety data

Type of Study	Study Identifier Protocol No.	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	No. Subjects Enrolled/ Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Duration of Study[a]	Study Status; Type of Report/ Location
Study Reports of Controlled Clinical Studies Pertinent to Claimed Indication (continued)								
Efficacy and Safety	20120263	Efficacy, safety, immunogenicity	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	350/347 (wk 16 analyses) 308/308 (re-randomized analyses) 350/347 (entire study analyses)	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, full CSR/ Module 5.3.5.1 (20120263)

Type of Study	Study Identifier Protocol No.	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	No. Subjects Enrolled/ Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Duration of Study[a]	Study Status; Type of Report/ Location
Ongoing Studies Not Included in the Marketing Application								
Long-term Safety and Efficacy	20130258	Efficacy, safety, immunogenicity	Phase 3, open-label, single arm extension of Study 20120262	ABP 501 40 mg SC, every other wk	467/Not included in marketing application	Randomized into Study 20120262 and completed wk 26 visit	72 wks	Ongoing
PK similarity	20120176	PK similarity, safety, tolerability, immunogenicity	Phase 1 randomized, single-blind, single-dose, 2-arm, parallel group	ABP 501 vs adalimumab (US) 40 mg SC, once	179 planned/ Not included in marketing application	Healthy male and female Japanese subjects, age 18 to 45 yrs BMI 16 to 25 kg/m2	63 days	Ongoing

BMI = body mass index; BSA = body surface area; CRP = C-reactive protein; CSR = clinical study report; ESR = erythrocyte sedimentation rate; EU = European Union; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥ 50% improvement in PASI; PK = pharmacokinetic; Ps = plaque psoriasis; RA = rheumatoid arthritis; SC = subcutaneous(ly); sPGA = Static Physician's Global Assessment; US = United States.
[a] Does not include screening.

No formal hypotheses were tested in the safety parts of the studies. The safety endpoints were treatment emergent adverse events (TEAEs) and serious adverse events (AEs), clinically significant changes in laboratory values and vital signs, and the incidence of ADAs.

The Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 (Study 20110217) or version 17.1 (Studies 20120262 and 20120263) were used for coding. The Common Terminology Criteria for Adverse Events (CTCAE) was used for grading adverse events.

Specific adverse events of interest for the safety analysis of the two Phase III studies were defined based on a review of product labels for the reference product Humira (US label and EU SmPC). These included: infections, malignancies, hypersensitivity reactions, demyelinating disease, haematological reactions, heart failure, lupus-like syndrome, liver enzyme elevations, and injection site reactions.

Comment: As this is a biosimilar application, the main purpose of the clinical safety section was to evaluate whether there are significant differences between the biosimilar and the reference product. The efficacy and safety of the reference product has been previously established for the currently approved indications.

8.2. Patient exposure

A summary of patient exposure to ABP 501 and to the reference product adalimumab (Humira) is provided in Table 28. Some subjects were exposed to both ABP 501 and adalimumab due to the study design in Study 20120263 which re-randomised some adalimumab subjects into the ABP 501 group.

The maximum duration of IP exposure was 48 weeks (Study 20120263 in psoriasis patients; median exposure: 330 days). RA patients were exposed to a maximum of 22 weeks in Study 20120262 (median exposure: 155 days). However, there is an open-label extension of Study 20120262 (named Study 20130258 and not part of this submission) in which RA patients continue until Week 72.

Table 28: Exposure to ABP 501 and adalimumab in 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).

8.2.1. Study 20120262 (RA patients)

The dose for all subjects (RA patients) was SC 40 mg IP every 2 weeks. Dose adjustments were not allowed, but in case of infection at a visit, the administration of IP could be delayed up to 3 days. 526 randomised subjects received at least 1 dose of IP. The overall mean dose received by subjects was 456.2 mg (SD: 75.4 mg). The overall dose and the exposure duration were similar for both treatment groups.

8.2.2. Study 20120263 (psoriasis patients)

The dose for all subjects (psoriasis patients) was an initial loading dose of SC 80 mg followed by SC 40 mg IP every 2 weeks. Dose adjustments were not allowed, but in case of infection at a visit, the administration of IP could be delayed up to 3 days.

The design of Study 20120263 was different to Study 20120262, as it had a Week 16 evaluation point, after which only patients with a PASI 50 response could continue, and at which approximately half of the adalimumab group was switched to ABP 501 after re-randomisation.

From baseline to Week 16, 174 subjects were treated with ABP 501 and 173 subjects were treated with adalimumab. Most subjects received 8 doses; 1 subject received 9 doses (adalimumab group). The overall mean (SD) dose received by subjects up to Week 16 was 350.3 mg (SD: 32.87 mg). The overall dose and the exposure duration were similar for both treatment groups.

Post Week 16, 308 subjects received at least 1 dose of IP: 152 subjects continued on ABP 501 (ABP 501/ABP 501), 79 subjects continued on adalimumab (adalimumab/adalimumab), and 77 subjects transitioned from adalimumab to ABP 501 (adalimumab/ABP 501). The overall mean (SD) dose received by subjects post Week 16 was 630.5 mg (SD: 131.69 mg). The overall dose and the exposure duration were similar for all three treatment groups.

8.2.3. Study 20110217 (PK study in healthy subjects)

The study subjects received a single 40 mg dose of either ABP 501, adalimumab (US), or adalimumab (EU). 67 subjects received ABP 501, 69 subjects received adalimumab (US), and 67 subjects received adalimumab (EU).

Comment: Patient exposure was adequate to show comparability to the reference product. Furthermore, a subset of Study 20120263 switched from adalimumab to ABP 501 providing safety for that scenario for a small group of subjects until Week 48 (32 weeks of data after switching).

8.3. Adverse events

The sponsor has not provided an integrated safety summary for the three submitted studies and provided the following reasons: difference in treatment duration, indication, concomitant methotrexate use between the studies. Instead, the safety data are presented for each study individually.

8.3.1. All adverse events and treatment-emergent adverse events (overview)

8.3.1.1. Study 20120262 (RA patients)

52.3% of all subjects had at least 1 adverse event, and this was similar in each treatment group (50.0% in the ABP 501 group and 54.6% in the adalimumab group). 20.0% had a TEAE (18.9%; 21.0%). 5 subjects had a TEAE with a Grade ≥ 3 (1.1%; 0.8%). An overall summary of AEs/TEAEs for this study is shown in Table 29.

Table 29: Study 20120262 Overall summary of adverse events by treatment (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)
Grade ≥3 AE	9 (3.4)	17 (6.5)	26 (4.9)
Treatment-related AE	50 (18.9)	55 (21.0)	105 (20.0)
Grade ≥3 Treatment-related AE	3 (1.1)	2 (0.8)	5 (1.0)
Serious AE	10 (3.8)	13 (5.0)	23 (4.4)
Treatment-related Serious AE	4 (1.5)	1 (0.4)	5 (1.0)
AE Leading to Discontinuation of IP	5 (1.9)	2 (0.8)	7 (1.3)
Treatment-related AE Leading to Discontinuation of IP	4 (1.5)	1 (0.4)	5 (1.0)
AE Leading to Discontinuation from Study	7 (2.7)	2 (0.8)	9 (1.7)
Treatment-related AE Leading to Discontinuation from Study	5 (1.9)	0 (0.0)	5 (1.0)

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

8.3.2. Study 20120263 (Psoriasis patients)

Up to Week 16, 65.4% of all subjects had at least 1 adverse event (67.2% in the ABP 501 group and 63.6% in the adalimumab group). 24.8% had a TEAE (24.7%; 24.9%). An overall summary of AEs/TEAEs for this study up to Week 16 is shown in Table 30.

Table 30: Study 20120263: Overall summary of adverse events by treatment up to Week 16 (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)

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.
Sources: Modified from Table 14-6.1.1.1 in Study 20120263 CSR

Using post Week 16 data, the proportion of all AEs was slightly lower in the adalimumab/adalimumab group (65.8%) compared to the ABP 501/ABP 501 (71.7%) and adalimumab/ABP 501 (70.1%) groups. However, the proportion of TEAEs was lowest in the ABP 501/ABP 501 group (18.4% versus 22.8% versus 26.0%). 12 subjects had a TEAE with a Grade ≥ 3 (4.6%; 2.5%; 3.9%). An overall summary of AEs/TEAEs for this study post Week 16 is shown in Table 31.

Table 31: Study 20120263 Overall summary of adverse events by treatment post-Week 16 (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.
Sources: Modified from Table 14-6.1.2.1 in Study 20120263 CSR

Table 32: Study 20120263 Overall summary of adverse events by treatment (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.

Source Dataset: ADAE, Program: t_oae.sas, Output: t14-06-001-003-001-ae-inc-saf.rtf, Generated on: 22MAY2015 08:39, Page 1 of 1

8.3.2.1. Study 20110217 (PK study in healthy subjects)

58.1% of all subjects had at least 1 adverse event. There were notable differences between groups in both AE and TEAE groups (Table 33). With regard to TEAEs, the percentages were 35.8% (ABP 501), 24.6% (adalimumab (US)), and 41.8% (adalimumab (EU)).

Table 33: Study 20110217 overall summary of adverse events by treatment (Safety Analysis Set)

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.
Source: Table 14.3.1.1 in Study 20110217 CSR

8.3.3. Common treatment-emergent adverse events

8.3.3.1. Study 20120262 (RA patients)

The most common adverse event by preferred term (≥ 5% overall) was nasopharyngitis (6.8%), and the proportions were similar between the two groups.

8.3.3.2. Study 20120263 (Psoriasis patients)

Up to Week 16, the most common adverse events by preferred term (≥ 5% overall) were nasopharyngitis (15.0%), headache (8.6%), and upper respiratory tract infection (5.2%), and the proportions were similar between the two groups.

Post Week 16, the most common adverse events by preferred term (≥ 5% overall) were nasopharyngitis (18.5%), upper respiratory tract infection (7.1%), and psoriasis (6.2%), and the proportions were similar across the 3 groups.

Across the entire study, the most frequently reported adverse events were similar between all treatment groups, including the group that underwent a single transition from adalimumab to ABP 501.

8.3.3.3. Study 20110217 (PK study in healthy subjects)

58.1% of subjects overall experienced any treatment emergent adverse event. All adverse events were Grade 1 or Grade 2, except for one Grade 3 dermoid cyst. The most common adverse event was headache (23.6%); all other adverse events had a subject incidence of less than 10%. Events were similar between the ABP 501 and adalimumab (US) groups. The adalimumab (EU) group appeared to have a greater incidence of TEAEs.

8.3.4. Deaths and other serious adverse events

8.3.4.1. Study 20120262 (RA patients)

No subject died in this study. Overall the proportion of subjects experiencing a serious treatment-emergent adverse event was 4.4%, 3.8% in the ABP 501 group and 5.0% in the adalimumab group. There were more cardiac disorders in the adalimumab group (4 counts compared to 1 in the ABP 501 group): 2 (0.8%) occurrences of myocardial infarction, one occurrence (0.4%) of congestive cardiac failure and one occurrence (0.4%) of worsening of Wolff-Parkinson-White syndrome (which was pre-existing). Some of the severe adverse events were deemed unrelated to the study drug (for example, humerus fracture or meniscus tear).

There were 2 (0.8%) subjects with infections/infestations in the ABP 501 group (compared to 3 (1.2%) in the adalimumab group). The two subjects in the ABP 501 both had sepsis related to IP: subject [information redacted] had a peritoneal abscess, appendicitis perforated and sepsis; subject [information redacted] had sepsis and pneumonia.

8.3.4.2. Study 20120263 (Psoriasis patients)

No subject died in this study. Overall, 23 of 347 subjects (6.6%) experienced serious TEAEs. Three subjects (13.6%) in the non-re-randomised ABP 501 treatment group experienced a total of 4 serious adverse events including acute myocardial infarction, arrhythmia, hypersensitivity, and lentigo maligna.

8.3.4.3. Study 20110217 (PK study in healthy subjects)

No subject died in this study. One serious adverse event was reported in the adalimumab (EU) group, but not in the ABP 501 group. The subject [information redacted] had a Grade 3 dermoid cyst deemed unrelated to the study drug and was withdrawn from the study due to this event.

8.3.5. Discontinuations due to adverse events

8.3.5.1. Study 20120262 (RA patients)

7 subjects (1.3%) discontinued IP due to a TEAE. 5 (1.9%) subjects were in the ABP 501 group and 2 (0.8%) subjects in the adalimumab group. One subject in the ABP 501 group experienced 2 TEAEs (pneumonia and hypertension) leading to discontinuation. The TEAEs in the ABP 501 group were pneumonia, cerebrovascular accident, and hypersensitivity. The TEAE in the adalimumab group was corneal graft rejection.

8.3.5.2. Study 20120263 (Psoriasis patients)

12 subjects (3.5%) discontinued IP due to a TEAE up to Week 16. 7 (4.0%) subjects were in the ABP 501 group and 5 (2.9%) subjects in the adalimumab group. 3 events in the ABP 501 group leading to discontinuation were serious adverse events (arrhythmia, hypersensitivity, and lentigo maligna).

11 subjects (3.6%) discontinued IP due to a TEAE post Week 16. The percentages per treatment group were 4.6%, 1.3%, and 3.9% in the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 groups, respectively. 2 serious TEAEs leading to discontinuation were: drug-induced liver injury (ABP 501/ABP 501) and ophthalmic herpes zoster (adalimumab/ABP 501).

8.3.5.3. Study 20110217 (PK study in healthy subjects)

There were no discontinuations (drug cessation) due to the study design (single dose study). However, a serious event of dermoid cyst resulted in study discontinuation (exit) in one subject.

8.4. Evaluation of issues with possible regulatory impact

Adverse events of interest in the Phase III studies were: infections, malignancies, hypersensitivity, demyelinating diseases, haematological reactions, heart failure, lupus-like syndrome, liver enzyme elevations, and injection site reactions.

An overview of the results of the adverse events of interest in the Phase III studies is shown in the following tables.

Table 34: Study 20120263 Adverse events of interest in subjects by treatment groups (Safety Analysis Set)

	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

AE = adverse event
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 35: Study 20120263 Adverse events of interest by treatment groups; Baseline to Week 16 (Safety Analysis Set)

	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.
Source: Table 14-6.7.1.1, Table 14-6.7.2.1, Table 14-6.7.3.1, Table 14-6.7.5.1. Table 14-6.7.8.1, Table 14-6.7.9.1

Table 36: Study 20120263 Adverse events of interest in subjects; post-Week 16 to end of study (Safety Analysis Set)

	Treatment Group A (ABP 501/ABP 501) (N = 152)		Treatment Group B1 (Adalimumab/Adalimumab) (N = 79)		Treatment Group B2 (Adalimumab/ABP 501) (N = 77)		Total (N = 308)	
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	Number of Subjects n (%)	Number of Events
Infections	67 (44.1)	105	29 (36.7)	51	37 (48.1)	62	133 (43.2)	218
Liver Enzyme Elevations	9 (5.9)	13	2 (2.5)	2	2 (2.6)	2	13 (4.2)	17
Hypersensitivity	8 (5.3)	10	2 (2.5)	2	3 (3.9)	4	13 (4.2)	16
Injection Site Reactions	2 (1.3)	2	3 (3.8)	6	0 (0.0)	0	5 (1.6)	8
Hematological reactions	0 (0.0)	0	1 (1.3)	2	1 (1.3)	2	2 (0.6)	4
Malignancies	1 (0.7)	1	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1

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.

8.4.1. Infections

8.4.1.1. Study 20120262 (RA patients)

Overall, 24.5% of subjects experienced any infection adverse event (ABP 501: 23.1%; adalimumab: 26.0%). The most commonly reported (≥ 5% overall) infection adverse event by preferred term was nasopharyngitis (ABP 501: 6.4%; adalimumab: 7.3%). Other events were upper respiratory tract infection (1.5% and 3.8%), and bronchitis (2.3% and 1.9%) in the ABP 501 and adalimumab treatment groups, respectively. There was 1 report of opportunistic infection (cytomegalovirus) in the ABP 501 group. There were no reports of invasive fungal infections. There were no cases of tuberculosis.

8.4.1.2. Study 20120263 (Psoriasis patients)

Up to Week 16, overall 33.7% of subjects experienced any infection adverse event, and the proportions were balanced between the 2 groups (ABP 501: 33.9%; adalimumab: 33.5%). The most commonly reported (≥ 5% overall) infection adverse events were nasopharyngitis (ABP 501: 14.4%; adalimumab: 15.6%) and upper respiratory tract infection (ABP 501: 5.2%; adalimumab: 5.2%).

Post Week 16, 43.2% of subjects experienced any infection adverse event (44.1%, 36.7%, 48.1% in the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 groups respectively). The most commonly reported (≥ 5% overall) infection adverse events by preferred term for the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 groups were nasopharyngitis (16.4%, 17.7%, 23.4%) and upper respiratory tract infection (5.9%, 7.6%, 9.1%).

There was one case of latent tuberculosis in the adalimumab group (Quantiferon positive), but deemed unrelated to adalimumab.

8.4.1.3. Study 20110217 (PK study in healthy subjects)

Overall, 10.8% of subjects experienced any infection adverse event (ABP 501: 13.4%; adalimumab (US): 5.8%, adalimumab (EU): 13.4%).

8.4.2. Malignancy

In clinical trials with TNF blockers, more cases of lymphoma were observed in patients in the TNF blocker group relative to the control group. Post-marketing cases of acute and chronic leukaemia have been associated with TNF blocker use.

8.4.2.1. Study 20120262 (RA patients)

3 events of malignancies in 2 subjects were reported: 1 subject in the ABP 501 group was diagnosed with basal cell carcinoma (left shoulder) and squamous cell carcinoma (left thigh),

and 1 subject in the adalimumab group was diagnosed with squamous cell carcinoma of the skin (cheek and scalp). None of these malignancies were reported as serious adverse events.

8.4.2.2. Study 20120263 (Psoriasis patients)

Up to Week 16, 2 events of malignancies in 2 subjects were reported: lentigo maligna in the ABP 501 group and Bowen's disease in the adalimumab group.

Post Week 16, a single malignancy event of squamous cell carcinoma (sebaceous adenoma) was reported for a subject in the ABP 501/ABP 501 group.

8.4.2.3. Study 20110217 (PK study in healthy subjects)

No malignancy was reported.

8.4.3. Hypersensitivity

Across the 2 studies in therapeutic indications, the proportion of hypersensitivity adverse events was similar between treatment groups, although the proportions seemed slightly larger in the ABP 501 group.

8.4.3.1. Study 20120262 (RA patients)

The overall proportion of subjects with hypersensitivity adverse events was 4.6%, (ABP 501: 5.3%; adalimumab: 3.8%).

8.4.3.2. Study 20120263 (Psoriasis patients)

Up to Week 16, the overall incidence of hypersensitivity adverse events was 4.3%, (ABP 501, 4.6%; adalimumab, 4.0%). Post week 16, the overall incidence of hypersensitivity adverse events was 4.2%, (ABP 501/ABP 501, 5.3%; adalimumab/adalimumab, 2.5%; adalimumab/ABP 501, 3.9%). One hypersensitivity event in the ABP 501 group was serious (Grade 4) and led to discontinuation of IP and study.

8.4.3.3. Study 20110217 (PK study in healthy subjects)

No hypersensitivity reaction was reported.

8.4.4. Demyelinating disease

No events classified as demyelination adverse events were reported.

8.4.5. Lupus-like syndrome

No events classified as lupus-like syndrome adverse events were reported.

8.4.6. Haematology and haematological toxicity

8.4.6.1. Study 20120262 (RA patients)

1.9% of subjects in both groups experienced a haematological adverse event. The only event in > 1% of subjects in either treatment group was leukopaenia (ABP 501: 1.5% (4/264), adalimumab: 1.1% (3/262)). None of the haematological reaction adverse events were reported as serious adverse events.

8.4.6.2. Study 20120263 (Psoriasis patients)

Up to Week 16, 3 subjects (0.9%) (adalimumab group) experienced haematological adverse events. Post week 16, 2 subjects (0.6%) (one in the adalimumab/adalimumab group and one in the adalimumab/ABP 501 groups) experienced haematological adverse events. None of the events were considered serious and none led to discontinuation of IP or to study discontinuation.

8.4.6.3. Study 20110217 (PK study in healthy subjects)

One case of lymphocytosis occurred in each the ABP 501 group and in the adalimumab (EU) group.

8.4.7. Immunogenicity and immunological events

8.4.7.1. Study 20120262 (RA patients)

5 of 264 subjects (1.9%) in the ABP 501 group and 6 of 262 subjects (2.3%) in the adalimumab group tested positive for pre-existing binding antibodies. No subjects tested positive for neutralising antibodies.

All 526 subjects had at least 1 evaluable antibody test result of ABP 501 or adalimumab and were included in the antibody analysis set. The overall percentage of subjects that developed binding ADAs was 38.2% (ABP 501: 38.3%; adalimumab: 38.2%. The percentage developing neutralising ADAs was 10.1% (ABP 501, 9.1%; adalimumab, 11.1%).

Using a statistical model adjusted for stratification factors, the difference in the percentage of developing binding ADAs between ABP 501 and adalimumab was 0.219% (90% confidence interval (CI (-6.795%, 7.234%)). The difference for neutralising ADAs was -1.434% (90% CI: (-6.741%, 3.874%)).

Table 37: Study 20120262 Antidrug antibodies summary results by treatment (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.
Source: Table 14-10.1.3 in Study 20120262 CSR

8.4.7.2. Study 20120263 (Psoriasis patients)

No subjects tested positive for pre-existing neutralising antibodies. With regard to pre-existing binding antibodies, no subjects in the non-re-randomised group tested positive, but in the re-randomised group, there was one subject in each of the 3 treatment groups that tested positive.

Up to Week 16, the overall percentage of subjects developing binding ADAs was 59.4% (ABP 501: 55.2%; adalimumab: 63.6%) and 11.8% for neutralising ADAs (ABP 501: 9.8%; adalimumab: 13.9%) (Table 38).

Table 38: Study 20120263 Antidrug antibodies summary results by treatment; through Week 16 (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.

Post Week 16, the overall percentage of subjects developing binding ADAs was 72.3% and 21.9% for neutralising ADAs. The percentage of developing binding or neutralising ADAs was as follows: binding ADAs: 68.4%, 74.7%, and 72.7%; neutralising ADAs: 13.8%, 20.3%, 24.7%, for ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 groups, respectively. The adalimumab/ABP 501 group had the largest proportion of subjects with neutralising ADAs (24.7%).

The difference in the percentage of subjects developing binding antibodies between ABP 501 and adalimumab was -8.122% with 95% CI of (-18.242%, 1.998%). The difference in the

percentage of subjects developing neutralising antibodies between ABP 501 and adalimumab was -3.531% with 95% CI of (-10.392%, 3.331%).

The evolution of ADA results throughout the study for each treatment group is shown in Table 39. It appears that, from Week 16 onwards, the proportion of ADA-positive subjects is consistently higher in the adalimumab/ABP 501 (single-switch) group.

Table 39: Study 20120263 Anti-drug antibodies results by visit and treatment; through entire study (ADA Analysis Set)

	Non Re-randomized		Re-randomized		
Visit Binding/Neutralizing	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 (%)
Baseline					
Binding					
ABP 501 Assay Positive	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (1.3)
Adalimumab Assay Positive	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	1 (1.3)
Positive in Either Assay	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	1 (1.3)
Neutralizing					
ABP 501 Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adalimumab Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Positive in Either Assay	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Week 4					
Binding					
ABP 501 Assay Positive	10 (45.5)	6 (35.3)	36 (23.7)	19 (24.1)	17 (22.1)
Adalimumab Assay Positive	10 (45.5)	7 (41.2)	36 (23.7)	18 (22.8)	18 (23.4)
Positive in Either Assay	10 (45.5)	7 (41.2)	40 (26.3)	22 (27.8)	19 (24.7)
Neutralizing					
ABP 501 Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adalimumab Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Positive in Either Assay	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Week 16					
Binding					
ABP 501 Assay Positive	13 (59.1)	8 (47.1)	63 (41.4)	40 (50.6)	42 (54.5)
Adalimumab Assay Positive	13 (59.1)	8 (47.1)	66 (43.4)	37 (46.8)	45 (58.4)
Positive in Either Assay	13 (59.1)	8 (47.1)	72 (47.4)	43 (54.4)	48 (62.3)
Neutralizing					
ABP 501 Assay Positive	4 (18.2)	3 (17.6)	9 (5.9)	7 (8.9)	8 (10.4)
Adalimumab Assay Positive	2 (9.1)	4 (23.5)	10 (6.6)	8 (10.1)	7 (9.1)
Positive in Either Assay	4 (18.2)	4 (23.5)	11 (7.2)	9 (11.4)	8 (10.4)
Week 20					
Binding					
ABP 501 Assay Positive			78 (51.3)	43 (54.4)	49 (63.6)
Adalimumab Assay Positive			73 (48.0)	46 (58.2)	46 (59.7)
Positive in Either Assay			83 (54.6)	47 (59.5)	50 (64.9)
Neutralizing					
ABP 501 Assay Positive			10 (6.6)	9 (11.4)	10 (13.0)
Adalimumab Assay Positive			11 (7.2)	9 (11.4)	8 (10.4)
Positive in Either Assay			11 (7.2)	9 (11.4)	10 (13.0)
Week 32					
Binding					
ABP 501 Assay Positive			66 (43.4)	39 (49.4)	46 (59.7)
Adalimumab Assay Positive			72 (47.4)	42 (53.2)	44 (57.1)
Positive in Either Assay			76 (50.0)	45 (57.0)	46 (59.7)
Neutralizing					
ABP 501 Assay Positive			8 (5.3)	7 (8.9)	8 (10.4)
Adalimumab Assay Positive			8 (5.3)	6 (7.6)	7 (9.1)
Positive in Either Assay			8 (5.3)	7 (8.9)	8 (10.4)
Week 52					
Binding					
ABP 501 Assay Positive			59 (38.8)	33 (41.8)	39 (50.6)
Adalimumab Assay Positive			62 (40.8)	32 (40.5)	41 (53.2)
Positive in Either Assay			65 (42.8)	34 (43.0)	42 (54.5)
Neutralizing					
ABP 501 Assay Positive			13 (8.6)	9 (11.4)	16 (20.8)
Adalimumab Assay Positive			13 (8.6)	9 (11.4)	16 (20.8)
Positive in Either Assay			13 (8.6)	10 (12.7)	16 (20.8)

8.4.7.3. Study 20110217 (PK study in healthy subjects)

No pre-existing ADAs were detected in the baseline samples. In the single-dose PK similarity study, the overall percentage of subjects developing binding ADAs was 58.6%; the values were

similar for the ABP 501 (53.7%) and adalimumab (US) (55.1%) groups but slightly higher for the adalimumab (EU) group (67.2%). With regard to neutralising antibodies, the values are 17.9%, 21.7%, and 20.9% for the ABP 501, adalimumab (US), and adalimumab (EU) groups, respectively.

Comment: Immunogenicity is one of the most important safety concerns in a biosimilar evaluation. Immunogenicity (through both neutralising and non-neutralising anti-drug-antibodies (ADAs)) has the potential to alter both efficacy and safety. However, the clinical significance of ADAs remains uncertain. Limited data shows that ADA positive patients are more likely to experience infusion reactions. The development of ADAs is not necessarily linked to non-responder patients. However, when comparing etanercept to adalimumab, it appears that adalimumab patients who develop ADAs have worse clinical outcome compared to those who do not develop ADAs (Krieckaert *et al*., 2012). It was expected that the percentage of ADA positive subjects would be overall lower in in the RA study compared to the psoriasis study due to concomitant methotrexate administration in the RA study. The psoriasis study population was better suited to detect any potential differences between treatment groups. A small literature review of anti-adalimumab antibodies (Hsu *et al*., 2014) revealed a proportion range of 6 to 45% of subjects tested which is lower compared to the results of the sponsor's psoriasis study. Different testing methods in the literature review studies may have contributed to the discrepancy, as the sponsor's study results revealed no significant differences between treatment groups. However, in the psoriasis study, the proportion of neutralising ADAs was slightly higher in the adalimumab/ABP 501 (single-switch) group post Week 16. Only 77 subjects switched from adalimumab to ABP 501. This makes it difficult to draw definite conclusions. But given that there is also a slight reduction in efficacy in this group between Week 32 to Week 50, this should be further monitored in the post-market environment, both as a potential efficacy and safety issue.

8.4.8. Injection site reaction

Across the 2 studies in therapeutic indications, injection site reaction adverse events were reported infrequently with a lower incidence in the ABP 501 arms than the adalimumab arms.

8.4.8.1. Study 20120262 (RA patients)

The overall percentage of subjects with injection site reaction adverse events was 3.6% (ABP 501: 2.3%; adalimumab: 5.0%).

8.4.8.2. Study 20120263 (Psoriasis patients)

Up to Week 16, the overall percentage of subjects with injection site reaction adverse events was 3.5% (ABP 501: 1.7%; adalimumab, 5.2%). Post week 16, the overall percentage was 1.6% (ABP 501/ABP 501: 1.3%; adalimumab/adalimumab: 3.8%; adalimumab/ABP 501: 0%).

8.4.8.3. Study 20110217 (PK study in healthy subjects)

One case of injection site rash occurred in each the ABP 501 group and in the adalimumab (EU) group.

8.4.9. Liver function and liver toxicity

As per study protocol, subjects with AST and/or ALT ≥ 2 times the upper limit of normal at baseline were excluded from the two Phase III studies.

Across the 2 studies in therapeutic indications, most of the liver enzyme elevation adverse events were Grade 1 or Grade 2 and only one liver enzyme elevation adverse event (drug induced liver injury) was serious.

8.4.9.1. Study 20120262 (RA patients)

There were 31 events of liver enzyme elevation in 4.4% of subjects (4.9% in the ABP 501 group and 3.8% in the adalimumab group). All of the liver enzyme elevation events were Grade 1 or Grade 2. One adverse event in a single subject (adalimumab group) resulted in an IP dose delay.

No case met Hy's law criteria.

8.4.9.2. Study 20120263 (Psoriasis patients)

Up to Week 16, the overall proportion of liver enzyme elevation adverse events was 1.7% (ABP 501: 2.3%; adalimumab: 1.2%). All of the liver enzyme elevation events were Grade 1 or Grade 2, except for one Grade 3 event in each treatment group which led discontinuation of IP and study discontinuation.

Post week 16, the overall incidence of liver enzyme elevation adverse events was 4.2% (ABP 501/ABP 501: 5.9%; adalimumab/ABP 501: 2.6%; adalimumab/adalimumab: 2.5%). One of those events was serious: a Grade 3 event of drug-induced liver injury (DILI) with concurrent increases in ALT and AST levels without change in bilirubin. The event started on Day 108 and resolved on Day 197. The event led to discontinuation of IP and to study discontinuation without liver enzyme levels decreasing which eventually occurred within 3 days of cessation of concomitant metoprolol and ramipril were discontinued. The DILI was resolved by the end of the study.

There was no evidence for an increase in liver-related event in subjects that switched from adalimumab to ABP 501.

8.4.9.3. Study 20110217 (PK study in healthy subjects)

No liver enzyme elevation events were observed in the ABP 501 group. However, 2 cases occurred in the adalimumab (EU) group.

8.4.10. Electrocardiograph findings and cardiovascular safety

The onset of new or the worsening of existing congestive heart failure is associated with TNF blockers, including adalimumab. Cases of worsening congestive heart failure, myocardial infarction, and cerebrovascular accident have been reported following adalimumab treatment.

A standard 12-lead ECG was performed during screening in Study 20120262, but no further study-related ECG measurements was performed. ECGs were not conducted in Study 20120263.

8.4.10.1. Study 20120262 (RA patients)

4 events of heart failure occurred in 0.6% of subjects (3/526), 1 in the ABP 501 group and 2 in the adalimumab group. One event of cardiopulmonary failure (ABP 501 group) and one event of congestive cardiac failure (adalimumab group) were reported as serious adverse events. The Grade 4 cardiopulmonary failure began on day 39 and resolved on day 48 following treatment with medication, and did not lead to IP or study discontinuation. However, concurrent hypertension and pneumonia lead to discontinuation of IP later on.

8.4.10.2. Study 20120263 (Psoriasis patients)

No events classified as heart failure adverse events were reported for subjects through the entire study.

8.4.10.3. Study 20110217 (PK study in healthy subjects)

There were no TEAEs related to ECG abnormalities. 6 subjects in the adalimumab (EU) treatment group had ECG abnormalities, but those were deemed normal or not clinically significant on repeat measurements.

8.4.11. Renal function and renal toxicity

8.4.11.1. Study 20120262 (RA patients)

Based on the data available, there were no clinically significant relevant differences between treatment groups. No laboratory abnormalities in renal function tests were reported as adverse events.

8.4.11.2. Study 20120263 (Psoriasis patients)

Based on the data available, there were no clinically significant relevant differences between the treatment groups. No laboratory abnormalities in renal function tests were reported as adverse events.

8.4.11.3. Study 20110217 (PK study in healthy subjects)

No laboratory abnormalities in renal function tests were reported as adverse events.

8.4.12. Vital signs and clinical examination findings

8.4.12.1. Study 20120262 (RA patients)

Overall, there were no clinically relevant changes seen post-baseline.

8.4.12.2. Study 20120263 (Psoriasis patients)

Overall, there were no clinically relevant changes seen post-baseline.

8.4.12.3. Study 20110217 (PK study in healthy subjects)

There were isolated cases of notable changes in blood pressure, diastolic blood pressure, pulse, and oral temperature, but those were deemed normal or not clinically significant on repeat measurements.

8.4.13. Other clinical chemistry

8.4.13.1. Study 20120262 (RA patients)

The median results for all other serum chemistry tests were within normal limits over the course of the study.

8.4.13.2. Study 20120263 (Psoriasis patients)

The median results for all other serum chemistry tests were within normal limits over the course of the study.

8.4.13.3. Study 20110217 (PK study in healthy subjects)

Shifts in chemistry laboratory results were not evaluated in Study 20110217.

8.5. Other safety issues

The sponsor provided the following statement:

> *'In accordance with regulatory guidances, safety studies in special groups and situations are not required and were not conducted (FDA, Draft Guidance for Industry, Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, 2015; World Health Organization, Guidelines on Evaluation of Similar Biotherapeutic Products [SBPs], 2009). Therefore, the following subsections are not included in this marketing application:*
>
> - *Intrinsic factors*
> - *Safety analyses in subjects with impaired renal function*
> - *Evaluations for biosimilar dose selection*

- *Safety of biosimilar candidate in other disease settings*
- *Extrinsic factors*
- *Drug interactions*
- *Use in pregnancy and lactation*
- *Overdose*
- *Drug abuse*
- *Effects of off treatment and retreatment*
- *Effects on ability to drive or operate machinery or impairment of mental ability'.*

In the safety analysis of the two clinical studies, subgroup analyses of adverse events by any of the following groups showed no clinically meaningful differences between treatment groups or when compared to the overall study population: prior biological use (for RA or psoriasis); age, race, and sex.

8.6. Post marketing experience

Not applicable to ABP 501, as currently not marketed in Australia or overseas.

8.7. Evaluator's overall conclusions on clinical safety

The reference product, adalimumab (Humira) has been marketed for more than a decade and the efficacy and safety has been established for the currently approved indications.

As this is a biosimilar application, the main purpose of the clinical safety section is to evaluate whether there are significant differences between the biosimilar and the reference product.

The sponsor has not provided an integrated safety summary, but presented the safety data for each study individually. The safety results from the two clinical studies were more representative with regard to target population and administration duration compared to the PK study which only administered a single dose in healthy subjects.

The maximum duration of IP exposure was 48 weeks in the psoriasis study and 22 weeks in the RA study. In the psoriasis study, the median exposure was 330 days and the overall mean dose was 456.2 mg. In the RA study, the median exposure was 155 days and the overall mean dose was 350.3 mg up to Week 16, and 630.5 mg post Week 16. The exposure was sufficient for comparability purposes. The clinical studies were not powered to detect rarer adverse events though.

8.7.1. Frequency and pattern of AEs and TEAEs

RA study: the percentage of AEs was similar in each treatment group (50.0% in the ABP 501 group and 54.6% in the adalimumab group). 20.0% had a TEAE (18.9%; 21.0%). 5 subjects had a TEAE with a Grade ≥ 3 (1.1%; 0.8%).

Psoriasis study: Up to Week 16, 65.4% of all subjects had at least 1 adverse event (67.2% in the ABP 501 group and 63.6% in the adalimumab group). 24.8% had a TEAE (24.7%; 24.9%). Post Week 16 data, the proportion of all AEs was slightly lower in the adalimumab/adalimumab group (65.8%) compared to the ABP 501/ABP 501 (71.7%) and adalimumab/ABP 501 (70.1%) groups. Regarding TEAEs, the proportions were 18.4% versus 22.8% versus 26.0%. 12 subjects had a TEAE with a grade ≥ 3 (4.6%; 2.5%; 3.9%).

8.7.2. Common adverse events

In both clinical studies, the most common adverse events by preferred term (≥ 5% overall) were nasopharyngitis, headache, upper respiratory tract infection, and (worsening of) psoriasis (psoriasis study only). The proportions were similar between the treatment groups, including the group that underwent a transition from adalimumab to ABP 501.

8.7.3. Deaths and serious adverse events

There were no deaths in any of the 3 studies provided.

RA study: There were 2 (0.8%) subjects with infections/infestations (sepsis) in the ABP 501 group and 3 (1.2%) in the adalimumab group.

*Psoriasis study***:** Overall, 23 of 347 subjects (6.6%) experienced serious TEAEs. Three subjects (13.6%) in the non-re-randomised ABP 501 treatment group experienced a total of 4 serious adverse events including acute myocardial infarction, arrhythmia, hypersensitivity, and lentigo maligna.

8.7.4. Discontinuations

RA study: 7 subjects (1.3%) discontinued IP due to a TEAE (1.9% versus 0.8%). The TEAEs in the ABP 501 group were pneumonia, cerebrovascular accident, and hypersensitivity. The TEAE in the adalimumab group was corneal graft rejection.

Psoriasis study: Up to Week 16, 12 subjects (3.5%) discontinued IP due to a TEAE (4.0% versus 2.9%). 3 events in the ABP 501 group leading to discontinuation were serious adverse events (arrhythmia, hypersensitivity, and lentigo maligna). Post week 16, 11 subjects (3.6%) discontinued IP (4.6%, 1.3%, 3.9%) (ABP 501/ABP 501, adalimumab/adalimumab and adalimumab/ABP 501). 2 serious TEAEs leading to discontinuation were: drug-induced liver injury (ABP 501/ABP 501) and ophthalmic herpes zoster (adalimumab/ABP 501).

8.7.5. Immunogenicity

Only a very small number of subjects tested positive for pre-existing binding ADAs in both studies. No subject had pre-existing neutralising antibodies. The proportion of subjects developing binding or neutralising ADAs was similar between treatment groups. In the RA study, binding ADAs were detected in 38.2%, neutralising ADAs was 10.1%. As expected the proportion of ADAs were lower in the RA study compared to the psoriasis study due to the concomitant methotrexate.

In the psoriasis study (up to Week 16), binding ADAs occurred in 59.4% (ABP 501: 55.2%; adalimumab: 63.6%) and neutralising ADAs in 11.8% for (9.8%; 13.9%). Post Week 16, the overall percentage of subjects developing binding ADAs was 72.3% and 21.9% for neutralising ADAs. The percentage of developing binding or neutralising ADAs was similar for all 3 groups (binding: 68.4%, 74.7%, and 72.7%; neutralising: 13.8%, 20.3%, 24.7%, for ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 groups, respectively). The results were reasonably similar between treatment groups. The proportion of both binding and neutralising ADAs appeared to be lower in the ABP 501 group.

However, in the psoriasis study, the proportion of neutralising ADAs was slightly higher in the adalimumab/ABP 501 (single-switch) group post Week 16. Only 77 subjects switched from adalimumab to ABP 501. This makes it difficult to draw definite conclusions. There is currently no evidence that the ADA development/immunogenicity in the single-switch group has led to clinically significant changes. But given that there is also a slight reduction in efficacy in this group between Week 32 to Week 50, this should be further monitored in the post-market environment, both as a potential efficacy and safety issue.

8.7.6. Adverse events of interest

Adverse events of interest in the clinical studies were: infections, malignancies, hypersensitivity, demyelinating diseases, haematological reactions, heart failure, lupus-like syndrome, liver enzyme elevations, and injection site reactions.

Liver function: No case met Hy's law criteria in the RA study. There was one Grade 3 event in each treatment group which led to discontinuation of IP in the psoriasis study. The ABP 501 group appeared to have higher proportions of liver enzyme elevation events, even this did not affect the group that switched to ABP 501 in the psoriasis study. One Grade 3 DILI event led to IP and study discontinuation. Even though the studies are not powered for safety purposes and even though the absolute numbers of cases were small, liver function should be specifically monitored in the post-market environment.

Haematological reactions: No serious haematological reaction adverse events occurred in the clinical studies.

Infections: In both the RA and psoriasis study, the infection adverse event proportions were similar between groups. Nasopharyngitis, upper respiratory tract infection, and bronchitis were most commonly reported. There was one opportunistic cytomegalovirus in the ABP 501 group (RA study). There were no reports of invasive fungal infections or tuberculosis. In the psoriasis study, there was one case of latent tuberculosis, but it was deemed unrelated to adalimumab. The rate and type of infection was consistent with known information on the reference product.

Malignancies: Each of the clinical study had a few cases of malignancy: in the RA study, there were one basal cell carcinoma and one squamous cell carcinoma (ABP 501) and one squamous cell carcinoma (adalimumab) which were non-serious. In the psoriasis study, there were two malignancy events: lentigo maligna (ABP 501) and Bowen's disease (adalimumab). Post Week 16, one squamous cell carcinoma occurred in the ABP 501/ABP 501 group. The rate and type of malignancy was consistent with known information on the reference product.

Hypersensitivity: the proportion of events was similar between treatment groups, although the proportions seemed slightly larger in the ABP 501 group (RA study: 5.3% versus 3.8%; Psoriasis study (up to Week 16) 4.6% versus 4.0%). In the psoriasis study (post Week 16) (ABP 501/ABP 501, 5.3%; adalimumab/adalimumab, 2.5%; adalimumab/ABP 501, 3.9%), one hypersensitivity event in the ABP 501 group was serious (Grade 4) and led to discontinuation of IP and study.

Heart failure: In the RA study 4 heart failure events occurred in 0.6% of subjects (3/526), 1 in the ABP 501 group and 2 in the adalimumab group. One event of cardiopulmonary failure (ABP 501 group) and one event of congestive cardiac failure (adalimumab group) were reported as serious adverse events. In the psoriasis study, no heart failure adverse events occurred.

Injection site reactions: Injection site reactions appeared to be less common in the ABP 501 arms.

There were no events classified as demyelinating disease, lupus-like syndrome, or renal toxicity.

Overall, the adverse event profile was fairly similar in all treatment groups. The safety data from the clinical studies and the PK study demonstrated that there were no clinically meaningful differences between ABP 501 and the reference product adalimumab. The clinical studies were not powered to provide statistical evidence of differences in less common adverse events.

The absence of a difference in the studies not powered for uncommon events does not provide evidence for the absence of safety concerns. There may be the possibility that the following are different in ABP 501 and this should be particularly monitored in the post-market environment and presented in PBRERs/PSURs: liver enzyme elevation; infections; hypersensitivity; ADA development/immunogenicity after switching from adalimumab (Humira) to ABP 501 (Amgevita).

Post-market monitoring is essential and the role of the risk management plan crucial in that regard. It is noted that the sponsor is conducting an open-label extension of the RA efficacy study. The study results should be used to contribute to the safety profile further, especially considering that currently there is no long term data ≥ 52 weeks available. Furthermore, as recommended in Section 7.7, disease registries should be utilised as well.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Rheumatoid arthritis	
Benefits	**Strengths and Uncertainties**
Equivalence of ABP 501 to Humira was shown for patients in moderate to severe rheumatoid arthritis (efficacy and safety).	*Strengths:* • Study 20120262 was very similar to the reference product pivotal trial with regard to study population and endpoints. The study design and its endpoints were based on a valid clinical model for rheumatoid arthritis. The ACR scores used are highly validated and composite endpoints. • Even though the original pre-determined equivalence margin was calculated to be relatively wide (0.738, 1/0.738), the primary endpoint also fulfilled the requirements of a more conservative, narrower margin (+/-15%) at 95% CI. • The equivalence is supported by the PK study results. *Uncertainties:* • Data was only available until Week 32. Longer term data were not available from Study 20120262; however, the study has an open-label extension up to 72 weeks which should be followed up as a post-authorisation efficacy study. • The concomitant use of another immunomodulator (methotrexate) which reduced the occurrence of immunogenicity may have had the potential to mask the difference in treatment effect between groups. • The signal-to-noise ratio with regard to treatment effect was relatively small. • Radiographic evidence was not part of the study. However, this may arguably only be necessary in a biosimilar application where the RA study is the only trial.
Psoriasis	
Benefits	**Strengths and Uncertainties**
Equivalence of ABP 501 to Humira was shown for patients in moderate to severe psoriasis (efficacy and safety).	*Strengths:* • Study 20120263 was very similar to the reference product pivotal trial with regard to study population and endpoints. The study design and its endpoints were mainly based on the current gold standard for psoriasis clinical trials, the PASI score. The pre-determined

Rheumatoid arthritis	
Benefits	**Strengths and Uncertainties**
	equivalence margin was reasonable at +/-15%. The reference product pivotal trial used PASI 75 (a categorical variable) as the primary endpoint, whereas Study 20120263 used the continuous PASI variable. This is often considered more suitable in equivalence trials, as more likely to detect smaller differences. Furthermore, there was no clinically significant difference with regard to the PASI 75 proportion comparison. • Longer term data were available, namely until Week 52 (48 weeks of study + 4 weeks follow-up). • The study did not allow subjects to use concomitant systemic immunomodulators. • The placebo-adjusted response rate (that is, signal-to noise ratio) with regard to treatment effect was larger than in the rheumatoid arthritis study. • The equivalence is supported by the PK study results. *Uncertainties:* No per-protocol analysis results were supplied for the study period post-Week 16. The study provided data on switching from Humira to ABP 501, but this was limited to 77 subjects and no definite conclusions on differences in efficacy and safety could be drawn. The psoriasis assessment tools are often considered a limitation of psoriasis clinical trials. Psoriasis assessments appear to be more subjective with clinicians often overestimating body surface area affected. The patient experience of severity is also rather subjective. The PASI's disadvantages are that the upper end of the scale is rarely used and may have low response distribution and no consensus on interpretability, whereas sPGA may not necessarily discriminate small change and may not have a robust range. However, the combination of validated psoriasis scores can mitigate some of the limitations.
Indications approved for the reference product Humira (other than rheumatoid arthtis or psoriasis)	
Benefits	**Strengths and Uncertainties**
Efficacy can be reasonably extrapolated from the conducted studies to the other indications approved for the reference product Humira	*Strengths:* • A high signal-to noise ratio indication (psoriasis) was used to detect potential differences between treatments, that is, to evaluate for equivalence. • The two clinical studies complemented each other: the RA study was a valid model for testing TNF-α antagonists and sufficiently robust and relevant to patients with other arthritides. The psoriasis study provided a better signal-to noise ratio and also a population more sensitive to immunogenicity making it better for extrapolation, and especially to extrapolation to IBD in that regard.

Rheumatoid arthritis	
Benefits	**Strengths and Uncertainties**
	• The dosing regimen used in the clinical studies was within the recommended dose range for all approved reference product adult indications. *Uncertainties:* • Not all indications were investigated. • The IBD indications may differ with regard to mechanism of action: The arthritis and psoriasis indications use the Fab region, whereas the Fc region may have a greater role in the IBD indications. • The dosing regimen used in the clinical studies differed from the approved reference product paediatric indications. • Malignancies (in particular lymphoma) have been associated with children and adolescents treated with TNF-α antagonists including adalimumab.

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
Concerns that efficacy and safety are not equivalent to the reference product in a real world setting	Strengths: • The clinical studies provided robust efficacy and safety data in the target indications. • Appropriate pharmacovigilance and risk minimisation measures should be implemented to detect, monitor and mitigate the risks. Uncertainties: • The clinical studies were not powered to detect more rare adverse events. • Uncertainties remain with regard to extrapolation to IBD and paediatric indications. • No data beyond 52 weeks are available. • Other unknown risks not detected in the provided studies, including loss of efficacy or new emerging safety signals.

9.3. First round assessment of benefit-risk balance

Overall, the benefit-risk balance of Amgevita (adalimumab, ABP 501) for the proposed usage is favourable. This assessment is based on the clinical data evaluated from a clinical point of view. The assessment was made by weighing up the risks and benefits as outlined in this evaluation report and summarised in the previous section. However, the favourable assessment is dependent on the satisfactory response to the evaluator questions, the agreement to implement an appropriate risk management plan, and a favourable assessment by the quality, toxicology, and RMP evaluators.

10. First round recommendation regarding authorisation

Approval of Amgevita (adalimumab, ABP 501) is recommended for the following indications (as per proposed Amgevita product information):

'Rheumatoid Arthritis

Amgevita is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

Amgevita can be used alone or in combination with methotrexate.

Polyarticular Juvenile Idiopathic Arthritis

Amgevita in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older 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.

Psoriatic Arthritis

Amgevita is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

Ankylosing Spondylitis

Amgevita is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's Disease in Adults and Children (≥6 years)

Amgevita is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients;

- *who have had an inadequate response to conventional therapies or,*
- *who have lost response to or are intolerant of infliximab.*

Ulcerative colitis

Amgevita is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time. (see Clinical Trials).

Psoriasis

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

However, the approval recommendation is dependent on the satisfactory response to the evaluator questions, the agreement to implement an appropriate risk management plan, and a favourable assessment by the quality, toxicology, and RMP evaluators.

It is noted the proposed indications for Amgevita do not include hidradenitis suppurativa. Hidradenitis suppurativa was added as an indication for the reference product Humira

(approved on 6 April 2016). The addition of hidradenitis suppurativa is also supported by the evaluator, that is, the following:

> *'Hidradenitis Suppurativa*
>
> *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 hidradenitis suppurativa therapy'.*

11. Clinical questions

11.1. Pharmacokinetics

No questions.

11.2. Pharmacodynamics

Not applicable.

11.3. Efficacy

1. In Study 20120262, no radiographic evaluations of joint damage progression (for example, using a Sharp/van der Heijde score) appear to have been used. The evaluator was unable to locate any radiographic data. Given that the radiographic claims in the Humira PI have been used in the proposed Amgevita PI, relevant data should be provided or a compelling justification be given.
2. In Study 20120263, the sponsor has conducted appropriate sensitivity analyses with the Per-protocol Analysis Set for the key efficacy endpoints up to Week 16. The evaluator was unable to locate the any per-protocol analyses for data beyond Week 16. The sponsor should provide these per-protocol analyses.
3. The sponsor has not provided a bridging study to link either Humira (US) or Humira (EU) to the Humira product supplied in the Australian market. The sponsor should provide confirmation that one of the Humira reference products tested is identical to the Australian-supplied product.
4. A small literature review of anti-adalimumab antibodies (Hsu *et al*., 2014) revealed a proportion range of 6–45% of subjects tested which is lower compared to the results of the sponsor's psoriasis study. The sponsor should comment on the discrepancy.

11.4. Safety

No questions.

12. Second round evaluation

12.1. Efficacy questions and answers

1. In Study 20120262, no radiographic evaluations of joint damage progression (for example, using a Sharp/van der Heijde score) appear to have been used. The evaluator was unable to locate any radiographic data. Given that the radiographic claims in the Humira PI have been

used in the proposed Amgevita PI, relevant data should be provided or a compelling justification be given.

Sponsor's response:

The sponsor confirms no radiographic evaluations of joint damage were included in ABP 501 Study 20120262 in subjects with moderate to severe rheumatoid arthritis (RA).

ABP 501 was developed as a biosimilar candidate to Humira (adalimumab). The regulatory pathway for approval of a biosimilar relies on demonstration of safety and efficacy data in an appropriate indication along with scientific justification to extrapolate to prior information regarding safety and efficacy data obtained by the originator. As the goal of biosimilar development is different from innovator development, the biosimilar candidate is not expected to show treatment effect against standard of care using the assessments that the originator had to demonstrate. Study 20120262 was conducted using sensitive and appropriate endpoints for assessment of similarity of ABP 501 and adalimumab with respect to efficacy. The totality of evidence has demonstrated similarity of ABP 501 and adalimumab, and similar results would be observed if measured by radiographic assessments.

The determination of clinical equivalence of ABP 501 and adalimumab support extrapolation to the full range of efficacy data in all indications for which adalimumab is approved, including the radiographic claims in the Humira (Australia) PI. Therefore, we submit that the language regarding the radiographic benefits should remain in the Amgevita PI.

Evaluator's comment:

Radiographic evaluations of joint damage are usually required for rheumatoid arthritis (RA) as a proposed indication where relevant statements are made in the product information document.

However, radiographic benefit may be reasonably extrapolated considering that equivalence in patients with moderate to severe rheumatoid arthritis (RA) was established in Study 20120262 using the validated indicators that had also been used in the originator trial (Keystone *et al.*, 2004), namely the ACR scores (with the risk ratio of ACR20 after 24 weeks being the primary endpoint in the equivalence trial). Furthermore, equivalence was also tested and supported separately in a non-arthritis condition.

As a result, there is no objection for the radiographic benefit statement to remain in the proposed product information document for Amgevita.

2. *In Study 20120263, the sponsor has conducted appropriate sensitivity analyses with the Per-protocol Analysis Set for the key efficacy endpoints up to Week 16. The evaluator was unable to locate the [any] per-protocol analyses for data beyond Week 16. The sponsor should provide these per-protocol analyses.*

Sponsor's response:

The sensitivity analyses using the per-protocol population for key efficacy endpoints up to and beyond Week 16 have been presented (see following tables):

- Psoriasis Area Severity Index (PASI) percent improvement from baseline.
- PASI 50
- PASI 75
- Static Physician's Global Assessment (sPGA)
- Psoriasis Body Surface Area (BSA)
- PASI 90
- PASI 100

The per-protocol analysis data up to Week 16 was included in the original marketing application to the TGA by initial treatments. The tables listed above are all-inclusive and by the randomised/re-randomised treatments.

These post hoc analyses beyond Week 16 were secondary and descriptive instead of inferential in nature; therefore, no sensitivity analysis was pre-specified for these analyses. Overall, all these sensitivity analyses support the conclusion of clinical similarity between ABP 501 and adalimumab.

The following tables summarise the provided Per-protocol Analysis Set data and compare them to the Re-randomised Analysis Set data provided in the initial dossier. Only the secondary endpoints in the initial dossier were considered, that is, Psoriasis Area Severity Index (PASI) percent improvement from baseline, PASI75, Static Physician's Global Assessment (sPGA), and Psoriasis Body Surface Area (BSA).

Table 40: Study 20120263 PASI percent improvement from Baseline at Weeks 32 and 50 (Re-randomised Analysis Set (observed cases) and Per-protocol Analysis Set (observed cases))

PASI percent improvement from baseline	Treatment difference between A and B1 (in %) (95% CI)	Treatment difference between B2 and B1 (in %) (95% CI)	Treatment difference between A and B1 (in %) (95% CI)	Treatment difference between B2 and B1 (in %) (95% CI)
	Re-randomised Analysis Set (observed cases)		Per-protocol Analysis Set (observed cases)	
Week 32	-0.49 (-5.60, 4.61)	1.05 (-6.93, 4.84)	0.07 (-4.98, 5.12)	-0.56 (-6.40, 5.27)
Week 50	-1.16 (-7.17, 4.86)	-2.37 (-9.26, 4.52)	-1.80 (-8.12, 4.53)	-1.56 (-8.83, 5.70)

Table 41: Study 20120263 PASI 75 response at Weeks 32 and 50 (Re-randomised Analysis Set (observed cases) and Per-protocol Analysis Set (observed cases))

PASI 75 response	Treatment difference between A and B1 (95% CI)	Treatment difference between B2 and B1 (95% CI)	Treatment difference between A and B1 (95% CI)	Treatment difference between B2 and B1 (95% CI)
	Re-randomised Analysis Set (observed cases)		Per-protocol Analysis Set (observed cases)	
Week 32	-2.751 (-13.935, 8.433)	0.582 (-12.899, 14.063)	-3.344 (-16.139, 9.451)	-1.090 (-15.417, 13.237)

PASI 75 response	Treatment difference between A and B1 (95% CI)	Treatment difference between B2 and B1 (95% CI)	Treatment difference between A and B1 (95% CI)	Treatment difference between B2 and B1 (95% CI)
Week 50	-4.680 (-15.263, 5.904)	-6.511 (-19.058, 6.037)	-5.241 (-16.517, 6.035)	-6.529 (-19.769, 6.712)

Table 42: Study 20120263 sPGA positive responses (0/1) at Weeks 32 and 50 (Re-randomised Analysis Set (observed cases) and Per-protocol Analysis Set (observed cases))

sPGA positive responses (0/1)	Treatment difference between A and B1 (95% CI)	Treatment difference between B2 and B1 (95% CI)	Treatment difference between A and B1 (95% CI)	Treatment difference between B2 and B1 (95% CI)
	Re-randomised Analysis Set (observed cases)		Per-protocol Analysis Set (observed cases)	
Week 32	-8.158 (-20.487, 4.171)	-4.195 (-18.099, 9.709)	-11.782 (-24.909, 1.346)	-6.428 (-21.014, 8.158)
Week 50	-9.636 (-22.328, 3.056)	-7.541 (-21.821, 6.738)	-9.991 (-23.772, 3.789)	-4.709 (-19.748, 10.331)

Table 43: Study 20120263 BSA involvement at Weeks 32 and 50 (mean change from baseline) (Re-randomised Analysis Set (observed cases) and Per-protocol Analysis Set (observed cases))

BSA involvement	Treatment difference between A and B1 (95% CI)	Treatment difference between B2 and B1 (95% CI)	Treatment difference between A and B1 (95% CI)	Treatment difference between B2 and B1 (95% CI)
	Re-randomised Analysis Set (observed cases)		Per-protocol Analysis Set (observed cases)	
Week 32	1.51 (-0.44, 3.46)	0.83 (-1.41, 3.07)	0.76 (-1.01, 2.53)	-0.05 (-2.08, 1.99)
Week 50	0.99 (-0.91, 2.90)	0.63 (-1.55, 2.81)	0.84 (-1.20, 2.88)	0.33 (-2.01, 2.68)

Evaluator's response:

The Per-protocol Analysis Set (per-protocol principle) provided a more conservative estimate of equivalence, and was therefore requested additional to the Re-randomised Analysis Set (intention-to-treat principle).

There seem to be no significant differences between treatment groups for 'PASI percent improvement from baseline' and 'BSA involvement'. This is the case for both the Re-randomised Analysis Set and the Per-protocol Analysis Set.

With regard to 'PASI 75 response' and 'sPGA positive responses (0/1)' treatment effect appears to be slightly lower in the ABP 501/ABP 501 group (group A). This is the case for both the Re-randomised Analysis Set and the Per-protocol Analysis Set, and more pronounced in the pre-protocol analysis, as expected.

The 'PASI percent improvement from baseline' and 'BSA involvement' involve continuous variables, whereas 'PASI 75 response' and 'sPGA positive responses (0/1)' involve categorical variables. Using categorical variables can be problematic and continuous variables are more suitable for equivalence trials (for example, to detect smaller differences in treatment effect). The secondary endpoints that used continuous variables produced a satisfactory result.

Overall, the results of the secondary efficacy endpoints were generally supportive of equivalence and efficacy throughout the study.

3. *The sponsor has not provided a bridging study to link either Humira (US) or Humira (EU) to the Humira product supplied in the Australian market. The sponsor should provide confirmation that one of the Humira reference products tested is identical to the Australian-supplied product.*

Sponsor's response:

As noted in the clinical evaluation report, a full justification demonstrating that Humira available in Australia is comparable to Humira available in the EU or US was provided in the initial submission to register Amgevita. The clinical evaluator notes that 'the justification will be evaluated', but no further comment is provided. It is therefore unclear whether the evaluator has specifically assessed the rationale.

The 'Australian Regulatory Guideline for Prescription Medicines, Regulation of Biosimilar Medicines' states that a 'bridging study may be abridged or omitted if you include evidence that the medicine is manufactured in a single site for global distribution'. The sponsor believes that the justification provided in the initial submission, together with further rationale provided in Response to Module 3 Question 26 [not provided here], provides sufficient evidence to demonstrate that Australian Humira is manufactured at a 'single site' for global distribution and that the Humira reference products tested are therefore the same as the Australian product. The criteria for not providing a bridging study, as cited in the guideline, have therefore been met.

The sponsor response to Question 26 by the TGA quality (Module 3) evaluator is as follows:

> 'The sponsor acknowledges that the 'Australian Regulatory Guideline for Prescription Medicines, Regulation of Biosimilar Medicines' states that where comparability studies do not use Australian reference product, a bridging study must be provided to demonstrate relevance to the Australian product. However, the guideline also states that a 'bridging study may be abridged or omitted if you include evidence that the medicine is manufactured in a single site for global distribution'. The ABP 501 biosimilar studies used non-Australian reference products (EU Humira and US Humira). Amgen believes that the justification provided in the current submission provides sufficient evidence to demonstrate that a bridging study to Australian Humira is not necessary.

Further evidence to support the arguments presented are as follows:

- Humira (adalimumab) is an innovator product marketed globally. While several manufacturing sites may be utilised for global supply of Humira, comparability between sites is required in order for each site to be registered. Once comparability is established between sites, Humira is considered the same irrespective of the site of manufacture. As such, Humira manufactured at different sites is considered the same product and for the purpose of compliance with the above-mentioned guideline can be considered as manufactured at a 'single manufacturing site'.
- The Australian drug substance manufacturing sites are no longer protected information given 5 years have passed since the goods have been registered. Under Section 25A(e) of the *Therapeutic Goods Act 1989*, Amgen requests that the TGA access the Australian Register of Therapeutic Goods for Humira to confirm the Australian drug substance manufacturing sites are the same as those registered in Europe, as shown in Humira SmPC 2016 Annex II A. This should confirm drug substance manufacture for the European reference product is the same as for the Australian product. Although the sites of European (or US) drug product manufacture are not publically available, drug substance manufacture is more relevant as a predictor of biological molecule similarity.

The sponsor has justified that the comparability studies presented in the marketing application meet the requirements of the 'Australian Regulatory Guideline for Prescription Medicine, Regulation of Biosimilar Medicines' by establishing that Humira (adalimumab) is manufactured at the same sites for global distribution. Furthermore, Amgen has demonstrated that Humira available in Australia has the same indications, and dosing regimen from the product available in the EU and US. Provision of a bridging study to demonstrate comparability of Humira available in Australia with the EU and US reference products is therefore not required'.

Evaluator's comment:

The clinical evaluator acknowledges the rationale and reasoning given by the sponsor. It is highly unlikely that Humira products in different countries with rather similar regulatory requirements (in this case: the US, the EU, and Australia) would be significantly different from each other, and that there would be significant clinical differences. Even though the sponsor's justification is acceptable for clinical evaluation purposes at this stage, the quality and non-clinical evaluator may require further evidence for their purposes.

4. *A small literature review of anti-adalimumab antibodies (Hsu et al., 2014) revealed a proportion range of 6 to 45% of subjects tested which is lower compared to the results of the sponsor's psoriasis study. The sponsor should comment on the discrepancy.*

Sponsor response:

The sponsor acknowledges the finding of lower incidence of anti-adalimumab antibodies in the literature as compared to the incidence of anti-drug antibody in the studies for ABP 501. The higher rates of anti-drug antibodies observed in ABP 501 clinical studies is the result of improvements in bioanalytical assays that now allow for anti-adalimumab antibodies that were always present in adalimumab-treated patients but are now detectable. Over the years, various improvements in label and signal detection such as chemiluminescent readouts and new electrochemiluminescent (ECL) plate-based technologies (for example, MSD) have extended assay sensitivity. In addition, procedural advances such as acid treatment (Patton *et*

al., 2005);[2] have reduced or eliminated the interfering high drug concentrations present in the serum sample.

The sponsor's methods utilize the electrochemiluminescent bridging immunoassay or ECLIA (Moxness et al., 2005[3]). This bridging immunoassay approach, extensively used in the clinical setting, detects all classes of ADA. In addition, the treatment of serum samples with acid to lower pH has been shown to dissociate ADA that may be bound by circulating drug levels, thus allowing the sensitive detection of ADA despite the presence of high drug concentrations. To ensure high assay sensitivity and high drug tolerance, Amgen implement this low pH acid treatment to detect ADAs to adalimumab and ABP 501. The higher rate of anti-adalimumab and anti-ABP 501 antibody incidence observed in our clinical studies is due to the use of the ECL platform in combination with acid dissociation. This has resulted in highly sensitive, specific and drug tolerant assays with a sensitivity of 25 ng/mL anti-adalimumab in presences of 20,000 ng/mL of drug. All samples tested in our clinical trials for binding antibodies are well below the drug tolerance of the assay, thus detecting all anti-adalimumab antibody responses.

Evaluator's comment:

The sponsor's response has been noted. The response is acceptable from a clinical point of view at this stage. However, post-market monitoring of immunogenicity/development of ADAs is essential.

12.2. Extrapolation to uveitis

After the first round evaluation phase for this application, an additional indication was approved by the TGA for the reference product Humira, namely the following:

> *'Humira is indicated for the treatment of non-infectious intermediate, posterior and pan-uveitis 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 sponsor is proposing to add uveitis as an indication for Amgevita, as indicated in their updated proposed product information (PI) wording. However, the sponsor has not commented on this addition in the dossier (outside the PI wording).

Evaluator's comment:

The conditions under which an extrapolation is reasonable (as outlined in Section: Efficacy above) apply, in the opinion of the clinical evaluator, to this indication, including the same dosing intervals in uveitis as for the psoriasis indication. Uveitis is often part of the spectrum of diseases for which adalimumab is already indicated (for example, uveitis as part of juvenile idiopathic arthritis (JIA)). TNFα, the target of adalimumab is found in synovial fluid, gut wall, and aqueous humour in patients with rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and uveitis respectively.

However, given the lack of suitable data, 'Long-term safety data in the treatment of adults with uveitis' should be added as missing information in the RMP.

[2] Patton A, Mullenix MC, Swanson SJ, Koren E 2005. An acid dissociation bridging ELISA for detection of antibodies directed against therapeutic proteins in the presence of antigen. *J Immunol Methods* 304:189– 195.
[3] Moxness M, Tatarewicz S, Weeraratne D, et al. 2005. Immunogenicity testing by electrochemiluminescent detection for antibodies directed against therapeutic human monoclonal antibodies. *Clin Chem* 51(10):1983–1985.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Amgevita (adalimumab, ABP 501) in the proposed usage are unchanged from those identified in the first round evaluation above.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Amgevita (adalimumab, ABP 501) in the proposed usage are unchanged from those identified in first round evaluation.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Amgevita (adalimumab, ABP 501), given the proposed usage, is favourable. This assessment is based on the clinical data evaluated from a clinical point of view. The assessment was made by weighing up the risks and benefits as outlined in this evaluation report.

14. Second round recommendation regarding authorisation

Approval of Amgevita (adalimumab, ABP 501) is recommended for the following indications (as per proposed Amgevita product information):

'Rheumatoid Arthritis

Amgevita is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

Amgevita can be used alone or in combination with methotrexate.

Polyarticular Juvenile Idiopathic Arthritis

Amgevita in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older 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.

Psoriatic Arthritis

Amgevita is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

Ankylosing Spondylitis

Amgevita is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's Disease in Adults and Children (≥6 years)

Amgevita is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients;

- *who have had an inadequate response to conventional therapies or,*
- *who have lost response to or are intolerant of infliximab.*

Ulcerative colitis

Amgevita is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time. (see Clinical Trials).

Psoriasis

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

Hidradenitis Suppurativa

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 hidradenitis suppurativa therapy.

Uveitis

Humira is indicated for the treatment of non-infectious intermediate, posterior and pan-uveitis 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'.

Note: the proposed indications from Amgevita differ from those found in the first round clinical evaluation report. The two additional indications were approved for the reference product, Humira, since the completion of the first round clinical evaluation report. As indicated above, there is no objection for an extrapolation to these two additional indications.

15. Second round comments on product documentation

15.1. Second round comments on draft PI (clinical aspects)

The sponsor has not provided a separate response item with regard to the PI recommendations in the first round clinical evaluation report. However, the sponsor has provided an updated, annotated, proposed PI document in which the recommended changes are incorporated. Below is an assessment of the PI changes in relation to the first round clinical evaluation report PI recommendations:

1. In the 'Indications' section, the sponsor should consider adding the hidradenitis suppurativa indication.

The sponsor has added the relevant indication to the 'Indications' section, and has also added the 'Uveitis' indication that has been recently approved for the reference product Humira:

Hidradenitis Suppurativa

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 hidradenitis suppurativa therapy.

Uveitis

Amgevita is indicated for the treatment of non-infectious intermediate, posterior and pan-uveitis 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.

15.1.1. Evaluator comment

It is recommended that the proposed insertion be approved.

2. *The reference product Humira has been updated to reflect the additional indication of hidradenitis suppurativa. The sponsor should align the PI document to accommodate the changes made. Even if the sponsor chooses not to include hidradenitis suppurativa as an indication for Amgevita, the PI sections other than the indication section should be updated to reflect the increase in trial data available (for example, in the 'Adverse Effects' section).*

The sponsor has made multiple additions to the PI to accommodate the recommendation. The sponsor has aligned the Amgevita PI document to include all the relevant changes made to the Humira PI document (Version 38) to accommodate for the hidradenitis suppurativa indication.

Furthermore, the sponsor has aligned the Amgevita PI document to include all the relevant changes made to the Humira PI document (Version 38) to accommodate for the uveitis indication.

15.1.2. Evaluator comment

It is recommended that the proposed insertions be approved.

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