Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Adalimumab

Proprietary Product Name: Amgevita

Sponsor: Amgen Australia Pty Ltd

June 2018

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 AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

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
DILI	Drug induced liver disease
DMARD	Disease-modifying anti-rheumatic drug
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate

Abbreviation	Meaning
EU	European Union
EULAR	European League Against Rheumatism
IBD	Inflammatory bowel disease
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

I. Introduction to product submission

Submission details

Type of submission:	Biosimilar medicine
Decision:	Approved
Date of decision:	18 October 2017
Date of entry onto ARTG	9 November 2017
Active ingredient:	Adalimumab
Product name:	Amgevita
Sponsor's name and address:	Amgen Australia Pty Ltd 115 Cotham Road Kew, VIC, 3101
Dose forms:	Pre-filled syringe and Pre-filled syringe with pen injector
Strengths:	20 mg/ 0.4 mL and 40 mg/ 0.8 mL
Container:	Pre-filled syringe
Pack sizes:	Amgevita 20 mg solution for injection in single-use pre-filled syringe: • Carton containing 1 pre-filled syringe • Carton containing 2 pre-filled syringes Amgevita 40 mg solution for injection in single-use pre-filled syringe or pre-filled SureClick pen (for patient use): • Carton containing 1 pre-filled syringe or pre-filled pen • Carton containing 2 pre-filled syringes or pre-filled pens • Carton containing 4 pre-filled syringes or pre-filled pens • Carton containing 6 pre-filled syringes or pre-filled pens.
Approved therapeutic use:	***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.* ***Juvenile Idiopathic Arthritis*** ***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 antirheumatic drugs (DMARDs). Amgevita can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-Related Arthritis

Amgevita is indicated for the treatment of enthesitis-related arthritis in children, who have had an inadequate response to, or who are intolerant to, conventional therapy.

Psoriatic Arthritis

Amgevita is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderately 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 in Adults and Children

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

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.
Route of administration:	Subcutaneous (SC)
Dosage:	This product is for one dose in one patient only. Same as for the innovator product Humira (see Attachment 1 for the PI)
ARTG numbers:	273536, 278701, 278702

Product background

This AusPAR describes the application by the sponsor to register Amgevita, which contains active ingredient adalimumab as a biosimilar to Humira.

Amgevita is proposed for the same indications approved for Humira: rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease in adults and children (≥ 6 years) and ulcerative colitis. The innovator, Humira received recent approval for a new indication, hidradenitis suppurativa (acne inversa) in April 2016. This application represents the first application in Australia for a biosimilar version of adalimumab, that is, for a biosimilar version of Humira.

Amgevita, like Humira, is administered through the SC route. It is supplied as pre-filled syringes that contain 20 mg adalimumab in 0.4 mL sterile solution (paediatric use formulation) or 40 mg adalimumab in 0.8 mL sterile solution for SC administration. Dose, frequency and duration of administration of Amgevita will be the same as for Humira and vary depending on the indication, with maximum dose proposed as 160 mg at fortnightly intervals for an unspecified duration.

Adalimumab is a recombinant human immunoglobulin G1 anti-tumour necrosis factor alpha (TNFα) monoclonal antibody. It binds to human 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.

While the clinical evaluation has a comprehensive list of relevant guidelines (see below and Attachment 2), guidelines of particular relevance are:

- The TGA specific guideline on the regulation of biosimilar medicines, Evaluation of biosimilars version 2.0, 17 December 2015;
- 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; and
- EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products containing monoclonal antibodies, non-clinical and clinical issues.

The biosimilar adalimumab proposed in this application is also referred to as ABP 501 in this AusPAR.

Regulatory status

This is an application to register a new biosimilar product on the Australian Register of Therapeutic Goods (ARTG).

The innovator product, Humira solution for injection which was approved for registration in December 2002 as 40 mg/0.8 mL vial, prefilled syringe and prefilled syringe with needleguard. 20 mg/0.4 mL presentations were subsequently approved.

At the time of submission Amgevita had not been approved in any other regulatory jurisdiction. It has now been approved in the United States (US) (23 September 2016). A submission has also been approved by the European Medicines Agency (EMA; 22 March 2017) and a submission was under consideration by the Health Canada.

The following table describes the innovator products registered on the ARTG.

Table 1: Humira products registered in Australia

Product	ARTG No	Relationship
Humira adalimumab (rch) 10 mg solution for injection pre-filled syringe	AUST R 216038	Innovator product.
Humira adalimumab (rch) 10 mg solution for injection pre-filled syringe (27 G)	AUST R 238700	Innovator product.
Humira adalimumab (rch) 20 mg solution for injection pre-filled syringe	AUST R 199411	Innovator product.
Humira adalimumab (rch) 40 mg solution for injection vial	AUST R 95779	Innovator product.
Humira adalimumab (rch) 40 mg solution for injection pre-filled syringe	AUST R 199412	Innovator product. EU and US equivalent used for comparability studies.
Humira adalimumab (rch) 40 mg solution for injection pre-filled pen.	AUST R 199410	Innovator product.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2: Registration timeline for Submission PM-2016-00845-1-1

Description	Date
Submission dossier accepted and 1st round evaluation commenced	3 May 2016
First round evaluation completed	5 October 2016
Sponsor provides responses on questions raised in first round evaluation	30 November 2016
Second round evaluation completed	9 January 2017
Request for Advisory Committee advice and/or Delegate's Overview	3 July 2017
Sponsor's response to Delegate's Overview	18 July 2017
Advisory Committee meeting	4 August 2017
Registration decision	18 October 2017
Entry onto ARTG	9 November 2017
Number of TGA working days from commencement of evaluation to registration decision*	245

* Target timeframe for standard applications: 220 working days. Statutory timeframe: 255 working days.

III. Quality findings

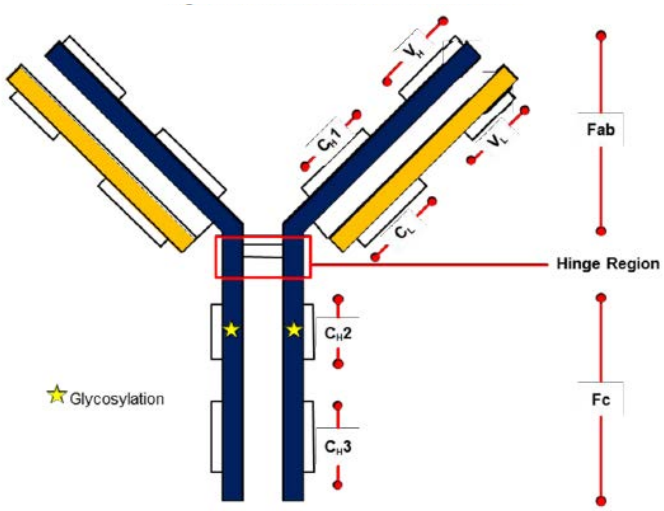
Drug substance (active ingredient)

Structure

ABP 501 is a fully human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass expressed in the Chinese hamster ovary (CHO) cell line and consists of 2 heavy chains (HC) and 2 light chains (LC) of the kappa subclass. ABP 501 contains 32 total cysteine residues involved in both intrachain and interchain 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 Asn301.

The molecular formula for the predominant ABP 501 HC isoform (C-terminal glycine) is $C_{219}1H_{3392}N_{582}O_{677}S_{15}$, not including N-linked glycans. The molecular formula for ABP 501 LC is $C_{1027}H_{1610}N_{282}O_{332}S_6$. The theoretical mass of glycosylated ABP 501 containing 2 N-linked glycans (1 per HC) is 148,081 Da. The experimentally determined predominant ABP 501 mass is 148,083 Da, which is in agreement with the theoretical value. A schematic diagram of ABP 501 is shown below in Figure 1.

Figure 1: Schematic diagram of ABP 501



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.

Biological activity

ABP 501 specifically binds to human TNFα and prevents it from binding to TNFα receptor 1 (TNFR1, p55TNFR, or TNFRSF1A) and TNFα receptor 2 (TNFR2, p75TNFR, or TNFRSF1B). The in vitro potency assay is a cell based apoptosis inhibition assay in which ABP 501 binds to recombinant purified human TNFα and inhibits it from binding to the TNFR and inducing apoptosis. ABP 501 also binds FcγRs and induces both antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in vitro.

Drug product

Apart from the active ingredient the drug product contains sucrose, polysorbate 80, glacial acetic acid, sodium hydroxide and water for injection.

The recommended drug product shelf life (include temperature excursion during shipping if necessary) is:

- 2°C to 8°C (5°C) for up to 6 months
- 14 days up to 25°C.[1] Once removed from the refrigerator for room temperature storage, Amgevita must be used within 14 days or discarded, even if it is returned to the refrigerator.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data demonstrates the product is not photostable.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Amgevita adalimumab.

[1] Note: this condition is only approved for product stored for the 6 month shelf life at 2 to 8°C.

All issues raised in the initial product summary have been resolved.

Proposed Conditions of Registration (for Delegate)

1. Batch Release Testing & Compliance with Certified Product Details (CPD)

   – It is a condition of registration that all batches of Amgevita™ adalimumab (rch) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

   – It is a condition of registration that each batch of Amgevita™ adalimumab (rch) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

   The sponsor must supply:

   a. Certificates of Analysis of all active ingredient (drug substance) and final product.

   b. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).

   c. Evidence of the maintenance of registered storage conditions during transport to Australia.

   d. Five (5) containers of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

IV. Nonclinical findings

Introduction

General comments

The scope of the nonclinical testing program for ABP 501 is in general accordance with the relevant accepted guidance on nonclinical testing of similar biological medicinal products.[2] Data presented consisted of comparative in vitro pharmacology studies on biosimilar adalimumab (referred to herein as ABP 501) relative to Humira comparators. As well, two Good Laboratory Practice (GLP) repeat dose toxicity studies were conducted in cynomolgus monkeys with concomitant toxicokinetic assessments.

The sponsor used European Union (EU) and US sourced Humira as comparators. Australian sourced Humira was not used in any of the nonclinical studies and bridging studies were not originally conducted to demonstrate sufficient similarities between the Australian product and comparators, which is required according to TGA guidance on the regulation of biosimilar medicines.[3] The sponsor cited various reasons for this omission including the possibility that Australian sourced Humira originates from a supplier common to the EU and US sourced Humira. Following additional discussions with the

[2] EMEA/CHMP/BMWP/42832/2005 Rev 1 – Guideline on similar biological medicinal products containing biotechnology- derived proteins as active substance: nonclinical and clinical issues.
EMA/CHMP/BMWP/403543/2010 – Guideline on similar biological medicinal products containing monoclonal antibodies – nonclinical and clinical issues.
[3] Biosimilar medicines regulation (http://www.tga.gov.au/publication/evaluation-biosimilars).

TGA's quality evaluation area, the sponsor acknowledged the need for bridging studies and submitted an analytical similarity assessment between Australian sourced and EU and US sourced Humira. The assessment was concluded to have demonstrated sufficient analytical similarity between the Australian sourced product and EU and US sourced comparators used in the dossier by the quality evaluator, therefore satisfied the TGA mandated requirement of bridging studies.

A number of in vitro comparability studies were included. These concerned the biological attributes of ABP 501 relative to EU and US sourced Humira (that is, TNFα binding affinity, apoptosis, ADCC, CDC activity) and are to be evaluated and assessed by the quality evaluator. Salient findings from these studies were summarised and ABP 501 appeared to exhibit adequate comparability to Humira with respect to various biological attributes (see below).

Pharmacology

Adalimumab is a monoclonal antibody that binds to human TNFα and confers anti-inflammatory activity by preventing the binding of TNFα to its soluble and membrane bound receptors. As a biosimilar, ABP 501 is expected to exhibit the same pharmacological actions as Humira. Since the pharmacological activity of adalimumab is already well characterised in the original assessment of Humira, the objective of primary pharmacology studies was to demonstrate comparable pharmacology of ABP 501 relative to comparator Humira. This was done as a series of in vitro studies with several lots of either ABP 501, EU and US sourced Humira.

Affinity of ABP 501 for soluble and membrane bound TNFα was comparable to Humira. Adalimumab is specific for human TNFα but also has affinity for primate (but not rodent) TNFα; thus demonstration of affinity for TNFα from cynomolgus monkey provided support for their use in toxicity studies. Assays to evaluate the effects of adalimumab on effector functions (as TNFα induced apoptosis/cytotoxicity and release of IL-8 by effector cells) found ABP 501 neutralised the actions of TNFα to a similar extent as Humira. Although there was considerable variability in activities for the cytotoxicity assays, range of inhibitory activity (as 50% effective concentration (EC_{50})) was similar among all three groups. A cell based assay ostensibly demonstrated an inability of ABP 501 to inhibit the LTα-induced release of cytokine IL-8 in cultured Human umbilical vein endothelial cells (HUVECs) as proof that ABP 501 does not interact with LTα; however, the study showed findings from two assays where one assay appeared to illustrate partial inhibition (approximately 30% inhibition) by ABP 501 relative to Humira comparators. In response to a question from the quality evaluator on this discrepancy, the sponsor submitted a new in vitro study that used an assay technique with improved sensitivity and specificity. The new study confirmed that, similarly to EU and US sourced Humira, ABP 501 does not inhibit LTα-induced IL-8 release by HUVECs and therefore has no activity against LTα.

Being an IgG1 immunoglobulin, interactions with the Fc-fragment part of adalimumab were also assessed to establish comparability of Fc receptor binding by ABP 501 relative to Humira comparators. Ranges of mean relative binding to Fcγ receptors RIa, RIIa (131H allele variant), RIIIa and FcRn were similar for ABP 501 and EU and US sourced Humira. Further assessment of binding for FcγRIIIa allele variants 158F and 158V, which have different affinities for IgG1- resulting in varied Fc- effector responses, also found no discernible differences between relative binding of ABP 501 and EU or US sourced Humira with either FcγRIII variant. Thus, ABP 501 is expected to interact with either FcγRIII allele variant comparably to Humira.

Additional studies on effector functions were also described in the sponsor's submission as part of similarity assessments on biological activity. Detailed analysis of these findings will be provided by the quality evaluator. The interaction between soluble TNFα and cell

surface TNFR1 receptors signals apoptosis, and antigen recognition and specificity (Fab fragment function) underpin the anti-apoptotic actions of adalimumab.

Relative potencies of ABP 501, EU and US sourced Humira as inhibitors of apoptosis were comparable in a cell based assay. However, limited details were provided on how these values were determined and concentration ranges were not specified. With regard to Fc-related effector functions, ADCC and CDC activities were assessed using cell-based fluorescence assays. For ADCC activity, CHO cells expressing membrane bound TNFα served as target cells while FcγRIII-presenting NK-92M1 were effector cells. ABP 501 was found to ably induce dose dependent increases in apoptosis and the range of relative activity was similar to that determined for EU and US sourced Humira. Although data on the affinity of adalimumab for complement C1q were not presented, data on CDC activity assays, which relate to effector functions resulting from this interaction, showed that ABP 501 evoked complement dependent cytotoxicity that was comparable to Humira; therefore, it can be inferred that C1q affinity may also be comparable. Recruitment of regulatory macrophages is an Fc-dependent effector response considered relevant to the efficacy of adalimumab, particularly for inflammatory bowel disease indications. Interaction of the Fc-region of TNFα-bound adalimumab and Fcγ receptors on T cells induces regulatory macrophages which promote mucosal healing and inhibit the proliferation of activated T cells.[4] With respect to ABP 501, this process was assessed in a mixed lymphocyte reaction (MLR) assay where all three adalimumab types inhibited T cell proliferation to some degree. Attenuation was slightly greater with the Humira lots than ABP 501 lots (range of adalimumab lot activities as percentage of control T cell proliferation: ABP 501: 72 to 86%; US Humira: 63 to 85%; EU Humira: 64 to 76%). The link between these findings with regulatory macrophage induction was not immediately evident as this was only shown using US sourced Humira. The study also did not disclose whether other mechanisms were investigated to rule out their role in the T cell effects (for example, apoptosis). In response to a query, the sponsor submitted additional data that examined reverse signalling activity as an alternative apoptotic mechanism relevant to the extrapolation of the inflammatory bowel disease (IBD) indications. The additional data indicated comparable apoptotic activity evoked by the different types of adalimumab in tmTNFα-expressing Jurkat cells. However, it did not address the original question of whether attenuations to T cell proliferation shown in Study R20140036 reflected the involvement of regulatory macrophages or was due to other mechanisms such as reverse signalling.

It was also noted in the same study that the extent of attenuation of T cell proliferation was slightly greater with US and EU sourced Humira than ABP 501. In response to a question, the sponsor explained that data points deemed as outliers were included in the final analysis of the original report but when these data points were excluded, the values of all adalimumab tested lots were comparable. Thus the sponsor considered ABP 501 comparable to the two Humira comparators with respect to attenuated T cell proliferation. In the nonclinical evaluator's view, the range of values ascertained were similar for all three of the different lots of ABP 501 and US and EU sourced Humira, even when factoring in the outliers; thus it is agreed that values that denoted T cell attenuation were, overall, similar between ABP 501 and EU and US sourced Humira.

Nonclinical demonstration of in vivo efficacy was not provided. According to the overarching EMA guideline on biosimilars;[5] the need for in vivo studies depends on the availability of a relevant in vivo model, which is consistent with the sponsor's reasoning

[4] Vos ACW, Wildenberg ME, Duijvestein M, Verhaar AP, Van den Brink GR & Hommes DW (2011). Anti-tumour necrosis factor–α antibodies induce regulatory macrophages in an Fc region-dependent manner. Gastroenterology, 140, 221–230.
[5] EMEA/CHMP/BMWP/42832/2005 Rev 1 – Guideline on similar biological medicinal products containing biotechnology- derived proteins as active substance: nonclinical and clinical issues.

that lack of adalimumab activity against rodent TNFα precluded the need for conducting in vivo studies in these species. The guideline suggests that there might be a need if there are sufficient differences that might predict differences in functional responses (for example, post-translational modification, use of unusual or novel excipients). Based on the in vitro dataset, there do not appear to be compelling reasons to warrant in vivo studies simply to demonstrate efficacy, especially considering the multiple indications proposed for the product.

The in vitro nonclinical data demonstrated mostly adequate comparability of ABP 501 to Humira with respect to its affinity and pharmacological activity against TNFα; although it is noted that the level of detail on experimental protocols (not analytical or validation methods) used in in vitro studies was limited. Also, comparable efficacy for regulatory macrophage induction may be uncertain as there were modest differences in the ability of ABP 501 to attenuate T cell proliferation compared to US and EU sourced Humira, an action ostensibly related to the induction of regulatory macrophages.

The quality evaluator also commented further on the comparability assessments including those that pertain to biological activity. Biological activity comparability assessments of ABP 501 were considered to have adequately demonstrated similarity to Humira, relative to criteria based on acceptance ranges. In a query on whether investigations were conducted to confirm that, like innovator Humira, ABP 501 is selective only for TNFα and has no affinity for TNFβ (also known as lymphotoxin α or LTα), the sponsor referred to their submitted Study R20120007 in which a functional assay was conducted as an index of adalimumab affinity for either TNFα or LTα. Briefly, IL-8 release by HUVECs in response to either (recombinant human) TNFα or LTα in the presence or absence of the different adalimumab forms was assessed. Summary findings of two assays (conducted on 2 separate days with data for each day presented as the mean of 3 assay replicates) showed variable results in which data from the first assay suggested some partial activity by ABP 501 against TNFβ, while the second assay showed lack of activity by ABP 501 comparable with the two Humira types. As mentioned above, the sponsor submitted a follow-up study after the second round evaluation which used an improved detection method to assess activity of ABP 501 against LTα-induced release of IL-8 (Study 20150129). This new study confirmed that ABP 501 was comparable to EU and US sourced Humira in its lack of effect on LTα-induced release of IL-8 by HUVECs.

Overall, all outstanding issues concerning the pharmacological attributes of ABP 501 relative to EU and US sourced Humira have been addressed and ABP 501 is concluded to exhibit sufficient pharmacological biosimilarity to EU and US sourced Humira.

Pharmacokinetics

Toxicokinetic assessments were determined using data from the two 1 month repeat dose toxicity studies in cynomolgus monkeys, including a shorter study that was terminated before term on Day 10. Both studies showed similar toxicokinetic parameters (peak plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC)) between ABP 501 and US sourced Humira. There were subtle differences in the range of peak sera times, with a greater range of times and therefore variability with ABP 501 but the median time to peak plasma concentration (T_{max}) for ABP 501 was the same as for US sourced Humira. Extent of accumulation was also similar between the two types of adalimumab (2.6 times and 2.4 times higher AUC exposures on Day 22 compared to Day 1 for ABP 501 and Humira, respectively), however this might be due to inappropriate sampling intervals used (Day 1 when median T_{max} is approximately 48 h).

Toxicology

Toxicity testing was limited to two 1 month GLP-compliant studies on comparative toxicity in cynomolgus monkeys. Either ABP 501/Amgevita or US sourced Humira were administered as weekly SC doses of either 32 mg/kg or 157 mg/kg. The lower dose study was terminated on Day 10 because of study design limitations (that is, no placebo control group and dose considered too low).

Consequently only 2 doses were administered and only limited parameters were recorded at up to Day 9 of treatment. The higher dose study was completed to term and included a full battery of in-life and post-mortem assessments. The choice of higher dose is acceptable as it provided sufficient multiples of human exposure (about 75 times the clinical exposure based on serum AUC comparisons from a single administration to the monkeys, and even higher exposure multiples after multiple administrations). Anti-drug antibody development was assessed only in the high dose study. It should be noted that the guideline recommends that toxicity testing should only be considered with appropriate justification where sufficiently high doses are used to compare toxicities of test biosimilar with reference product.[6] While the second study fulfils this requirement, comparative toxicity studies are generally not recommended for biosimilars unless there are reasons to suggest different quality attributes between the biosimilar and comparator, a point acknowledged by the sponsor.

In the study completed to term there were no mortalities or adverse clinical signs noted in any of the animal groups. Serum chemistry and urinalysis measurements were comparable, while haematological assessments indicated transient elevations in leukocyte and neutrophil counts in the Humira treated groups which resolved by Day 29. The transient changes to leukocytes in the Humira group are likely to be isolated and spontaneous occurrences as they have not been reported in previous toxicity studies with Humira.[7] In response to an enquiry, the sponsor considered these transient changes as minor differences that likely reflected individual biological variability and stated that in some animals predose levels of leukocytes and neutrophils were already high. As well, the sponsor pointed to the fact that leukocyte and neutrophil levels in both adalimumab treated groups were comparable to controls by Day 29 when serum AUC was approximately 2.5 fold higher than at the beginning of the study and so it was unlikely that these changes had a pharmacological basis. Furthermore, adalimumab related changes to leukocyte or neutrophil counts are not documented in the approved Product Information document for Humira, which the sponsor pointed as evidence that the leukocyte and neutrophil findings were incidental.

Necropsy assessments did not uncover findings in the ABP 501 group that were distinct from Humira or placebo treated animals. There were no treatment related differences in organ weights or gross findings. Histopathology findings showed mild to moderate decreases in germinal centre sizes of lymphoid tissues (axillary and mesenteric lymph nodes and tonsils) in all groups, which were higher in incidences in the ABP 501 and Humira groups. Evaluation of injection sites did not reveal test article reactions distinct from Humira or placebo treated groups. Anti-drug antibodies were not detected in any of the adalimumab-treated animals, but the sponsor indicated that the detection method may have been affected by circulating levels of adalimumab and thus the findings are unlikely to reflect the immunogenic potential of ABP 501 under clinical use conditions. Indeed incidence of anti-ABP 501 antibody development in patients was similar to anti-Humira

[6] EMA/CHMP/BMWP/403543/2010 – Guideline on similar biological medicinal products containing monoclonal antibodies – nonclinical and clinical issues.
[7] US FDA Pharmacology Review for HUMIRA®
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/Approval Applications/TherapeuticBiologicApplications/ucm092772.pdf)

antibody development. Overall, in vivo toxicity studies did not identify any unexpected toxicity findings with ABP 501 or any findings inconsistent to those seen with Humira.

Local tolerance

Local tolerance per se of ABP 501/Amgevita at the SC injection site was not assessed, which is acceptable as per guideline recommendation;[8] advising against such studies unless the product contains excipients for which there is limited experience or understanding with the clinical route. All excipients included in ABP 501/Amgevita have an established history of use with the SC route. There were no adverse findings reported in either of the two monkey studies (up to 4 weeks treatment) which might suggest poor local tolerance of ABP 501 in the clinic.

Paediatric use

As with Humira, the sponsor has also proposed a number of paediatric indications (Crohn's disease in children ≥ 6 years and juvenile idiopathic arthritis) for ABP 501/Amgevita. There were no new nonclinical studies in juvenile animals. This is not considered a deficiency as the primary objective of the testing strategy for biosimilar substances is to establish comparability to the innovator biological substance, as outlined in the guideline for similar biological medicinal products containing monoclonal antibodies.[9]

Nonclinical summary and conclusions

- The scope of the nonclinical testing program was in general accordance with EU guidelines on similar biological medicines. Data consisted of comparative studies on the pharmacology and toxicity of biosimilar adalimumab (ABP 501) against comparators EU and US sourced Humira.
- Pharmacological activity of ABP 501, as assessed in a series of in vitro binding and functional assays, was generally comparable to Humira comparators. In response to a question, new data showed apoptotic activity ascribed to reverse signalling (potentially relevant to extrapolation of IBD indications) by ABP 501 were comparable to Humira comparators. A few subtle differences for some of the characteristics were likely limitations of the study designs per se, rather than a reflection of pharmacologically relevant differences between the biosimilar and Humira comparators.
- Four week GLP comparative toxicity studies were conducted in cynomolgus monkeys using the clinical (SC) route. An initial study was terminated early due to study design flaws. A second study used a higher dose of adalimumab (as ABP 501 or US sourced Humira) and attained high multiples of human exposure (at least 75 times the clinical exposure based on serum AUC comparisons). The study did not identify any unexpected toxicity findings with ABP 501 or findings inconsistent with those seen with Humira. Toxicokinetic parameters were comparable between the biosimilar and comparator. There were no adverse findings in monkeys that indicated poor local tolerance of ABP 501.
- Based on nonclinical studies submitted and additional information provided by the sponsor in response to questions after the second round evaluation, all major concerns

[8] EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products containing monoclonal antibodies: nonclinical and clinical issues.
[9] EMEA/CHMP/BMWP/42832/2005 Rev 1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues.

identified in the two rounds of nonclinical reports have been resolved. Nonclinical demonstration of comparative in vitro pharmacology, toxicokinetics and toxicity findings between ABP 501 and EU and US sourced Humira are generally acceptable and there are no nonclinical objections to registration.

- Amendments to the draft Product Information were recommended to the Delegate but the details of these are outside the scope of this AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Evaluator's commentary on the background information

Lack of a 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 (CD) 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 indication, 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.

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.

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.

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 was provided by the sponsor and evaluated.

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.

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 Rev 1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues
- 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

Contents of the clinical dossier

Scope of the clinical dossier

The dossier does not contain a full development program. The sponsor supports their biosimilar application with three bioequivalence as follows:

- 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).

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.[10]

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

Studies 20110217, 20120262, and 20120263 provided pharmacokinetic (PK) data (as shown in Table 2, below).

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.

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

Table 2: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary PK aim of study
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§ - Multidose	20120262	To demonstrate pharmacokinetic similarity of ABP 501 to Humira by comparing steady state trough concentrations in patients with rheumatoid arthritis
	Target population§ - Multidose	20120263	To demonstrate pharmacokinetic similarity of ABP 501 to Humira by comparing steady state trough concentrations in patients with psoriasis

† indicates bioequivalence of different formulations; § indicates 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: 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.

Evaluator's 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 PI document have previously been accepted by the TGA. Consequently, the 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.

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.

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.

Efficacy

Studies providing efficacy data

Two studies provided evaluable efficacy data, described below.

Rheumatoid arthritis

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

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).

Evaluator's conclusions on 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 TNFα antagonist biosimilars used rheumatoid arthritis as their main study indication.[11]

The investigation of medicines for rheumatoid arthritis has a better choice of endpoints: the American College of Rheumatology (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,

[11] Lai Z, La Noce A 2016. Key design considerations on comparative clinical efficacy studies for biosimilars: adalimumab as an example. RMD Open 2(1):e000154

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;[12] 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 Static Physician's Global Assessment (sPGA) may not necessarily discriminate small change and may not have a robust range.[13] In the relevant EU guideline;[14] a combination of endpoint measures is recommended (for example, PASI and sPGA; or PASI and body surface area (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 clinical evaluator's opinion both were needed to establish the biosimilar status in ABP 501.

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.

Safety

Studies providing 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 (see *Scope of the clinical dossier* above and Table 3 below).

A summary of the studies providing safety data is in Table 3. Studies 20130258 and 20120176 were ongoing at the data lock point date and not part of this submission.

[12] Psoriasis Area and Severity Index (PASI) is the most widely used tool for the measurement of severity of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).
[13] Feldman S, Krueger G 2005. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis* 64(Suppl 2): ii65–ii68.
Spuls PI, Lecluse LL, Poulsen ML, Bos JD, Stern RS, Nijsten T 2010. How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review. J Invest Dermatol 130(4):933–943
[14] CHMP/EWP/2454/02 corr.

Table 3: 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)

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 Anti-drug antibodies (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 Summary of Product Characteristics (SmPC)). These included: infections, malignancies, hypersensitivity reactions, demyelinating disease, haematological reactions, heart failure, lupus-like syndrome, liver enzyme elevations and injection site reactions.

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.

Patient exposure

A summary of patient exposure to ABP 501 and to the reference product adalimumab (Humira) is provided in Table 4. 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 intraperitoneal (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 4: Exposure to ABP 501 and adalimumab in all clinical studies

Study Type Study No.	Number of Subjects Receiving at Least 1 Dose			
	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).

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 (standard deviation (SD): 75.4 mg). The overall dose and the exposure duration were similar for both treatment groups.

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 intraperitoneally (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.

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).

Patient exposure was adequate to show comparability to the reference product. Furthermore, a subset of Study 20120263 patients 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).

Postmarketing data

Not applicable to ABP 501 as it is currently neither marketed in Australia, nor overseas.

Evaluator's conclusions on 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.

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, 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%).

Common adverse events

In both clinical studies, the most common AEs 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.

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.

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 (DILI; ABP 501/ABP 501) and ophthalmic herpes zoster (adalimumab/ABP 501).

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.

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 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 AE 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 AEs.

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 Periodic Benefit Risk Evaluation Report (PBRERs)/ Periodic Safety Update Reports (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, disease registries should be utilised as well.

First round benefit-risk assessment

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, nonclinical and risk management plan (RMP) evaluators.

First round recommendation regarding authorisation

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

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, nonclinical 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.

Second round benefit-risk assessment

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.

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 the first round evaluation.

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.

Second round recommendation regarding authorisation

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

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.

VI. Pharmacovigilance findings

Risk management plan

- The sponsor has submitted EU RMP version 1.0 (21 October 2015; data lock point (DLP) 8 May 2015) and Australian Specific Annex (ASA) version 1.0 (22 March 2016) in support of this application. In its response to the first round RMP evaluation, the sponsor has submitted EU RMP version 1.2 (dated 7 November 2016; DLP 8 May 2015) and ASA version 2.0 (dated 18 November 2016).
- The sponsor has submitted ASA version 3.0 (dated 14 February 2017) with its response to the second round RMP evaluation.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below with the additional Australia-specific Missing Information agreed by the sponsor. Changes made from EU RMP version 1.0 to 1.2 are denoted by strikethrough (deletions) or underline (additions):

Table 5: Summary of ongoing safety concerns

R=routine and A=additional

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Serious infections including diverticulitis and opportunistic infections, e.g. invasive fungal infections, parasitic infections, legionellosis, and tuberculosis	✓	–	✓	✓
	Reactivation of hepatitis B	✓	–	✓	✓
	Pancreatitis	✓	–	✓	–
	Lymphoma	✓	–	✓	✓

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Hepatosplenic T-cell lymphoma	✓	–	✓	✓
	Leukemia	✓	–	✓	✓
	Non-melanoma skin cancer	✓	–	✓	✓
	Melanoma	✓	–	✓	✓
	Merkel cell carcinoma	✓	–	✓	✓
	Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)	✓	–	✓	✓
	Immune reactions – lupus-like reaction	✓	–	✓	–
	Immune reactions – allergic reactions	✓	–	✓	–
	Sarcoidosis	✓	–	✓	–
	Congestive heart failure	✓	–	✓	✓
	Myocardial infarction	✓	–	✓	–
	Cerebrovascular accident	✓	–	✓	–
	Interstitial lung disease	✓	–	✓	–
	Pulmonary embolism	✓	–	✓	–
	Cutaneous vasculitis	✓	–	✓	–
	Stevens-Johnson Syndrome	✓	–	✓	–
	Erythema multiforme	✓	–	✓	–
	Worsening and new onset of psoriasis	✓	–	✓	–
	Hematologic disorders	✓	–	✓	–
	Intestinal perforation	✓	–	✓	–
	Intestinal stricture in Crohn's disease	✓	–	✓	–
	Liver failure and other liver events	✓	–	✓	–
	Elevated alanine aminotransferase levels	✓	–	✓	–
	Autoimmune hepatitis	✓	–	✓	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Medication errors and maladministration	✓	–	✓	–
Important potential risks	Other malignancies (except lymphoma, hepatosplenic T-cell lymphoma, leukemia, non-melanoma skin cancer, and melanoma)	✓	–	✓	✓
	Vasculitis (noncutaneous)	✓	–	✓	–
	Progressive multifocal leukoencephalopathy	✓	–	✓	–
	Reversible posterior leukoencephalopathy syndrome	✓	–	✓	–
	Amyotrophic lateral sclerosis	✓	–	✓	–
	Colon cancer in ulcerative colitis patients	✓	–	✓	✓
	Infections in infants exposed to adalimumab in utero	✓	–	✓	–
	Off-label use	✓	–	✓	–
Missing information	Use in pregnant and lactating women	✓	–	✓	–
	Long term safety information in the treatment of children, ~~aged from 4 years to less than 18 years with psoriasis and~~^ from 6 years to less than 18 years with Crohn's disease	✓	–	✓	–
	Subjects with immune-compromised conditions either due to underlying conditions (i.e. diabetes, renal or liver failure, human immunodeficiency virus infection, alcohol or illicit drug abuse), or due to medications (postcancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications	✓	–	✓	–
	Remission-withdrawal-retreatment non-radiographic axial spondyloarthritis/axial spondyloarthritis without radiographic evidence of axial spondyloarthritis, and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis, and polyarticular juvenile idiopathic arthritis	✓	–	✓	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Long-term safety data in the treatment of adults with hidradenitis suppurativa^^	✓	–	✓	–
Australian-specific missing information	Subjects with poorly controlled medical conditions such as uncontrolled diabetes or documented history of recurrent infections, unstable ischaemic heart disease, chronic heart failure (CHF), recent cerebrovascular accidents	✓	–	✓	–
	Subjects with a history of cancer, lymphoma, leukaemia or lymphoproliferative disease; subjects with history of neurologic symptoms suggestive of demyelinating disorders	✓	–	✓	–
	Use in children < 18 years of age for ankylosing spondylitis, psoriasis and enthesitis-related arthritis	✓	–	✓	–
	Use in children < 6 years of age for enthesitis-related arthritis*	✓	–	✓	–
	Patients taking concomitant biologic therapy	✓	–	✓	–
	Long-term rheumatoid arthritis data beyond 10 years	✓	–	✓	–
	Long-term juvenile idiopathic arthritis data beyond 7.5 years	✓	–	✓	–
	Long-term ankylosing spondylitis data beyond 5 years	✓	–	✓	–
	Long-term axial spondyloarthritis data beyond 1 year	✓	–	✓	–
	Short- and long-term peripheral spondyloarthritis data	✓	–	✓	–
	Short- and long-term paediatric enthesitis-related arthritis data	✓	–	✓	–
	Long-term psoriatic arthritis data beyond 3 years	✓	–	✓	–
	Long-term psoriasis data beyond 6 years	✓	–	✓	–
	Long-term Crohn's disease data beyond 5 years	✓	–	✓	–
	Long-term paediatric Crohn's disease data beyond 2 years*	✓	–	✓	–
	Long-term ulcerative colitis data	✓	–	✓	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Short and long-term uveitis data	✓	–	✓	–

^Missing Information removed from the EU RMP version 1.2; ^^ Missing Information added to the EU RMP version 1.2; *Added in ASA version 3.0 (dated 14 February 2017).

- One additional pharmacovigilance activity is planned: Study (ABP 501) 20160264: An observational study to evaluate long-term safety of Amgevita/Solymbic in patients with rheumatoid arthritis. This is an overseas registry based study that will not include Australian patients.
- Additional risk minimisation activities include a patient alert card (adult and child), Safety Monograph, TB screening checklist and a guide for healthcare professionals prescribing Amgevita regarding latent tuberculosis infection. The activities proposed are the same as those required for the innovator product.

New and outstanding recommendations post second round evaluation

There is one minor outstanding issue:

Recommendation 13: As requested, the sponsor has added the wording regarding there not being a 10 mg presentation available to the Safety Monograph. However, the placement of this wording is at the very end of the monograph, after all the References and in the paragraph starting with the wording '*For more information on Amgevita, to report any adverse events involving Amgevita or to request additional copies of this material please contact Amgen Medical Information on 1800 803 638'*. It is recommended that the statement regarding the lack of a 10 mg presentation be included in *Section 1: Introduction.*

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The sponsor has provided an updated ASA (version 3.0) in its response to the second round RMP Evaluation, which has been satisfactorily revised.

Therefore the suggested wording is:

The EU-RMP (version 1.2, dated November 2016, data lock point 8 May 2015), with Australian Specific Annex (version 3.0, dated 14 February 2017), and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There are no objections on quality grounds to the approval of Amgevita adalimumab. All issues raised in the initial product summary have been resolved.

Based on nonclinical studies submitted and additional information provided by the sponsor in response to questions, all major concerns identified in the first and second round nonclinical reports have been resolved. Nonclinical demonstration of comparative in vitro pharmacology, toxicokinetics and toxicity findings between biosimilar adalimumab (referred to herein as ABP 501) and EU and US sourced Humira are generally acceptable and there are no nonclinical objections to registration.

The molecular formula for the predominant adalimumab HC isoform (C-terminal glycine) is $C_{2191}H_{3392}N_{582}O_{677}S_{15}$, not including N-linked glycans. The molecular formula for ABP 501 LC is $C_{1027}H_{1610}N_{282}O_{332}S_6$. The theoretical mass of glycosylated ABP 501 containing 2 N-linked glycans (1 per HC) is 148,081 Da.

The experimentally determined predominant ABP 501 mass is 148,083 Da, which is in agreement with the theoretical value.

ABP 501 specifically binds to human TNFα and prevents it from binding to TNFα receptor 1 (TNFR1, p55TNFR, or TNFRSF1A) and TNFα receptor 2 (TNFR2, p75TNFR, or TNFRSF1B). The in vitro potency assay is a cell-based apoptosis inhibition assay in which ABP 501 binds to recombinant purified human TNFα and inhibits it from binding to the TNFR and inducing apoptosis. ABP 501 also binds FcγRs and induces both antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in vitro.

The stability data provided was insufficient to justify a 36 month expiry period for product stored at 2°C to 8°C. Based on the current information provided, the TGA will assign a shelf life of only 6 month at 2°C to 8°C. The sponsor has agreed to this condition. Any subsequent application submitted post approval to extend the shelf life beyond 6 months at 2°C to 8°C must include real time stability data supporting the room temperature condition. This study should be performed at worst case scenario.

Nonclinical

There were no nonclinical objections to registration of adalimumab (Amgevita).

Based on nonclinical studies submitted and additional information provided by the sponsor in response to questions, all major concerns identified in the first and second round nonclinical reports have been resolved. Nonclinical demonstration of comparative in vitro pharmacology, toxicokinetics and toxicity findings between ABP 501 and EU and US sourced Humira are generally acceptable and there are no nonclinical objections to registration.

The scope of the nonclinical testing program for ABP 501 is in general accordance with the relevant accepted guidance on nonclinical testing of similar biological medicinal products.[2] Nonclinical data presented consisted of comparative in vitro pharmacology studies on ABP 501 relative to Humira comparators. As well, two GLP repeat dose toxicity studies were conducted in cynomolgus monkeys with concomitant toxicokinetic assessments. The sponsor used EU and US sourced Humira as comparators.

Australian sourced Humira was not used in any of the nonclinical studies and bridging studies were not originally conducted to demonstrate sufficient similarities between the Australian product and comparators, which is required according to TGA guidance on the regulation of biosimilar medicines.[3] The sponsor cited various reasons for this omission including the possibility that Australian sourced Humira originates from a supplier common to the EU and US sourced Humira.

Following additional discussions with the quality evaluation area, the sponsor acknowledged the need for bridging studies and submitted an analytical similarity assessment between Australian sourced and EU and US sourced Humira. The assessment

was concluded to have demonstrated sufficient analytical similarity between the Australian sourced product and EU and US sourced comparators used in the dossier by the quality evaluator, therefore satisfied the TGA mandated requirement of bridging studies.

Pharmacological activity of ABP 501 as assessed in a series of in vitro binding and functional assays, was generally comparable to Humira comparators. In response to a question, new data showed apoptotic activity ascribed to reverse signalling (potentially relevant to extrapolation of IBD indications) by ABP 501were comparable to Humira comparators. A few subtle differences for some of the characteristics were likely limitations of the study designs per se, rather than a reflection of pharmacologically relevant differences between the biosimilar and Humira comparators.

Clinical

There were no clinical objections to approval for all current indications of Humira, 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, nonclinical and RMP evaluators.

Three clinical studies comparing Amgevita to the reference product, Humira were submitted:

- Study 20110217: a Phase I, 3 arm parallel group, randomised, single blind, single dose PK similarity study that compared ABP 501 (Amgevita) 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).

At the request of the regulatory authority in Japan the sponsor agreed to perform another PK study to determine the PK bioequivalence of Amgevita and adalimumab in 179 healthy adult Japanese subjects. No results for this study were submitted with the current application.

Pharmacology

Pharmacokinetic (PK) data were available from each of the submitted studies. Bioequivalence with respect to C_{max} and AUC of subcutaneously administered Humira sourced from the USA and sourced from the EU with Amgevita was demonstrated in Study 20110217. Subgroup and sensitivity analyses also supported bioequivalence. This study is described in the CER (see Attachment 2).

Population Pk (PopPK) data were available from multiple dose studies in patients with rheumatoid arthritis (Study 20120262) and psoriasis (Study 20120263). Mean summary trough concentrations over time for test and reference adalimumab products are shown in the CER (see Attachment 2).

Efficacy

Study 20120262 was a double blind, parallel group, randomised, active comparator controlled, equivalence study in 526 adalimumab-naïve subjects with moderate to severe

RA. Subjects also received stable doses of methotrexate (MTX) and stable doses of oral corticosteroid were permitted. Efficacy and safety of Amgevita was compared with Humira (US). This study is described in the CER (see Attachment 2). Study duration was up to 30 weeks comprised: up to 4 weeks for screening and randomisation; a 22 week double blind dosing period with assessment of the primary efficacy endpoint 2 weeks after the last dose in the double blind period (Week-24); and a safety follow-up period for 2 weeks after the last dose of adalimumab.

The main inclusion criteria were: adults with active RA (2010 American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) criteria for moderate to severe RA) for at least 3 months; positive for rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP); and receipt of MTX for ≥ 12 weeks and on a stable dose for ≥ 8 weeks prior to administration of study drug. Notable exclusion criteria were: prior use of ≥ 2 biological therapies; and prior use of Humira or of a biosimilar adalimumab.

Subjects received either Amgevita 40 mg SC or Humira 40 mg SC on Day 1 and every 2 weeks (± 3 day dose window, for example, in case of infection) until Week 22. Subjects continued on a stable dose of MTX (≥ 7.5 mg/week, oral, or SC) unless side effects required a lower dose. Oral corticosteroid at a dose of ≤ 10 mg prednisone (or equivalent) per day was permitted provided the subject was on a stable dose for 4 weeks or more prior to initiation of study treatment.

The primary efficacy endpoint was the risk ratio (RR) of ACR20 at Week 24. The ACR20 is widely used in clinical rheumatology trials and presents at least a 20% improvement in a core set of measures assessing RA symptoms. Secondary efficacy endpoints included: change from Baseline in Disease Activity Score 28-CRP (DAS28-CRP); RR of ACR20 responses at Weeks 2 and 8; and RR of ACR50 and ACR70 responses at Week 24.

The primary efficacy analysis was of the intent-to-treat (ITT) population. The per protocol analysis was a sensitivity analysis for selected key efficacy endpoints. Last observation carried forward (LOCF) was used to accommodate missing data. Clinical equivalence was to be concluded if the 90% CI for ACR20 RR was (0.738, 1/0.738). The equivalence margin was calculated using methodology as suggested by the FDA draft guidance for industry and is accepted.[15] A detailed discussion of the methodology is in the statistical methods in the CER (see Attachment 2).

A total of 526 subjects (264 Amgevita, 262 Humira) were enrolled, randomised and received at least 1 dose of investigational product. 494 subjects (93.9%) completed the study. The groups had similar demographic and disease characteristics at Baseline. Mean age was 55.9 years (range, 21 to 80 years) and 81.0% were female. Mean duration of RA was 9.39 years. Mean baseline ACR scores were not provided however mean baseline DAS28-CRP (a disease activity score using C-reactive protein) was from 5.59 and 5.7 in the 2 treatment groups. 91.8% were positive for rheumatoid factor. More than 70% of subjects had not received a biological therapy for RA prior to this study, approximately half had been using oral corticosteroids and more than 60% had been using non-steroidal anti-inflammatory drugs (NSAIDs). The mean dose of MTX was 16.89 mg/week Amgevita versus 16.56 mg/week Humira.

Results were within the pre-defined limits for equivalence. At Week 24, 74.6% of subjects (194/260) given Amgevita and 72.4%(189/261) given Humira met the ACR20 response criteria. The RR of ACR20 for Amgevita/ Humira was 1.039 (2-sided 90% CI: 0.954, 1.133). This was within the predefined equivalence margin of (0.738, 1/0.738). Clinical equivalence was also demonstrated in the per protocol analysis: RR of ACR20 at Week 24 was 1.009 (90% CI: 0.927, 1.098; 95% CI: 0.912, 1.115). Secondary efficacy endpoint

[15] Non-Inferiority Clinical Trials (March 2010) (FDA, 2010).

results are shown in the CER (see Attachment 2) and also support clinical similarity of clinical outcomes for Amgevita and Humira.

Study 20120263 was a double blind, randomised, active comparator controlled study in 350 subjects with moderate to severe psoriasis. This study comprised:

- a screening period of up to 4 weeks;
- a double-blind period of 14 weeks in which subjects received either Amgevita or Humira (sourced from the EU). The primary efficacy assessment was 2 weeks after the last dose of study drug at Week 16;
- re-randomisation of subjects who were PASI 50 responders (defined as ≥ 50% improvement) at Week 16. Subjects initially randomised to Humira re-randomised to either continue Humira or switch to Amgevita. Subjects initially randomised to Amgevita continued treatment. Subjects were then followed for a further 34 weeks of blinded treatment;
- final efficacy assessment at Week 50 (2 weeks after last dose of study drug) and final safety assessment at Week 52.

The main inclusion criteria were: adults with stable moderate to severe plaque psoriasis for at least 6 months; psoriasis affecting ≥ 10% BSA with Psoriasis Area and Severity Index (PASI) ≥ 12 and static Physician's Global Assessment (sPGA) ≥ 3 and failure of at least 1 conventional anti-psoriatic systemic therapy. The PASI combines assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease). Details of its calculation are included in the CER (see Attachment 2).

The major exclusion criteria were: erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (for example, eczema); and previously use of 2 or more biological agents for treatment of psoriasis; previous use of adalimumab, or a biosimilar of adalimumab.

The dose regimen of adalimumab in both study groups was the recommended regimen for psoriasis, that is an initial loading dose of 80 mg SC on Week 1/Day 1, followed by 40 mg SC every other week starting 1 week after the loading dose (Week 2 and every 2 weeks thereafter).

The primary efficacy endpoint was the PASI percent improvement from Baseline at Week 16. Equivalence was assessed only for the primary efficacy endpoint. The primary analysis was of the ITT population and used LOCF for missing data. The per protocol (PP) analysis was provided and the equivalence margin provided for both ITT and PP analyses. Clinical equivalence of the primary endpoint was evaluated by comparing the 2-sided 95% CI of using a pre-specified equivalence margin of (-15, 15). The 2-sided 95% CI of the group difference was estimated using an Analysis of Covariance (ANCOVA) model. Covariates were baseline PASI score and stratification factors (geographic region and prior biologic use for psoriasis).

The equivalence margin was calculating using similar methodology to that of Study 20120262. Briefly, from published studies in psoriasis 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'*.

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.

A total of 350 subjects were randomised and 326 (93.1%) completed the study to Week 16 with data from 345 subjects included in the primary analysis of efficacy. The two treatment groups were balanced with respect to demographic and disease characteristics. Mean age was 44.6 years (range, 18 to 74 years), 65.1% were male, and 92.6% were Caucasian. The mean duration since diagnosis of psoriasis was 20.09 years, mean PASI score was 20.08 (a PASI score > 20 is considered severe disease) and the mean BSA affected by psoriasis was 26.9%. A total of 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.

Results were within the pre-defined limits for equivalence. For the ITT analysis, at Baseline, mean PASI scores were 19.85 for subjects given Amgevita (n = 175) and from 20.34 for subjects given Humira (n = 175). At Week 16 mean PASI scores were 3.74 for subjects given Amgevita (n = 172, an 80.91% reduction) and 3.29 for subjects given Humira (n = 173; an 83.06% reduction). The treatment difference for % improvement in mean PASI score from Baseline to Week 16 was -2.18 (95% CI -7.39, 3.02). The PP analysis (observed data) also demonstrated clinical equivalence with the PASI % improvement from Baseline 82.62% for Amgevita and 85.34% for Humira. The between group difference was -2.64 (95% CI -6.20, 0.91). Secondary efficacy assessments in the first 16 weeks of the study were also supportive of similarity of outcome for the two treatments. Subjects with prior use of biological agents had similar responses to those without prior use in both treatment groups.

At Week 16 of subjects initially randomised to Amgevita 87% (152/175) and 89% (156/175) were PASI 50 responders who continued to the second part of the study. Subjects on Amgevita continued and those who had received Humira were re-randomised with 79 continuing Humira and 77 switching to Amgevita. Treatment effect was maintained in all 3 treatment groups with (observed cases). At Week 32, the mean PASI % improvement from baseline was 87.62%, 88.16% and 86.98% in subjects given Amgevita/Amgevita; Humira/Humira; and Humira/Amgevita respectively.

At Week 50 the mean PASI % improvement from baseline was 87.16%, 88.11% and 85.82% in subjects given Amgevita/ Amgevita; Humira/ Humira; and Humira/ Amgevita respectively. All the between group comparisons for mean change in PASI % from Baseline in this stage of the study were within the 95%CI for equivalence that was determined for the primary efficacy endpoint, that is, within ±15%. Subject retention was good with the Week 50 efficacy analysis based on 134 subjects given Amgevita/Amgevita; 70 given Humira/Humira; and 69 given Humira/Amgevita respectively.

Safety data from the two equivalence studies has not shown clinically significant differences in any of the safety outcomes assessed. Due to the small numbers of subjects assessed it is possible that significant differences in less frequent adverse effects are present between the two products. The safety assessment of most interest is immunogenicity. Data on the presence of neutralising antibodies in 77 subjects who switched from Humira to Amgevita at Week 16 was presented for comparison with subjects continuing Amgevita to Week 52. An extract of Table 14-10.2.3 from the study report showing immunogenicity results over time in Study 20120263 is shown below as Table 6.

Table 6: Anti-drug antibodies summary results by treatment for ABP 501 or adalimumab assay through entire study (ADA analysis set)

Variable	Non Re-randomized		Re-randomized			
	ABP 501 (N = 22) n (%)	Adalimumab (N = 17) n (%)	ABP 501/ ABP 501 (N = 152) n (%)	Adalimumab/ Adalimumab (N = 79) n (%)	Adalimumab/ ABP 501 (N = 77) n (%)	Total (N = 347) n (%)
Subjects with an On-study Result[a]	22	17	152	79	77	347
Total Antibody Incidence [n (%)]						
Binding Antibody Positive Anytime	18 (81.8)	14 (82.4)	105 (69.1)	59 (74.7)	57 (74.0)	253 (72.9)
Neutralizing Antibody Positive Anytime	13 (59.1)	7 (41.2)	21 (13.8)	16 (20.3)	19 (24.7)	76 (21.9)
Subjects with a Result at Baseline [n (%)]	22	16	149	78	74	339
Pre-existing Antibody Incidence						
Binding Antibody Positive at or Before Baseline	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	1 (1.3)	3 (0.9)
Neutralizing Antibody Positive at or Before Baseline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Baseline is defined as the last non-missing assessment taken prior to the first dose of study IP.
[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 PsO and region.
[c] Negative result at the subject's last time point tested within the study period.

While there is no clear increase in immunogenicity with switching from Humira to Amgevita the subject numbers are too small to draw conclusions.

Risk management plan

There were no RMP objections to approval. The RMP evaluator is satisfied with version 3 of the Australian-specific Annex to the Risk Management Plan.

The RMP evaluator has noted the changes to the indications for the innovator adalimumab in Australia and that these additional indications will affect the content of the PI for Amgevita.

Risk-benefit analysis

Delegate's considerations

Clinical aspects of this submission were well presented. The single dose PK study showed bioequivalence of Amgevita and Humira for C_{max} and AUC. The two clinical equivalence studies were well designed, used appropriate clinical endpoints, adequately justified the equivalence margins and convincingly demonstrated clinical equivalence for subjects with rheumatoid arthritis and subjects with plaque psoriasis.

The sensitivity of assessment of clinical equivalence is likely to be higher in the plaque psoriasis population because those individuals were not also taking MTX which would have reduced both the difference in response to treatment with a biological agent and potentially masked differences in immunogenicity. Immunogenicity over 52 weeks was assessed only in the plaque psoriasis population and that was appropriate. There was no signal for increased immunogenicity on switching in the limited data provided.

Evaluation of this submission was prolonged due to a requirement for additional quality data to be submitted. Quality and nonclinical issues are now resolved.

While there are no clinical issues regarding the function of Amgevita it is not clear that all indications for Humira are able to be approved for Amgevita due to patent issues. New indications for Humira were approved during the course of evaluation of this submission. The most recent being enthesitis-related arthritis (ERA). The approach taken to these indications will impact on the content of the PI for Amgevita. At this stage the Delegate intends to proceed as if all indications were able to be approved. Should this not be the case, further review of the PI will be required.

Summary of Issues

While quality issues have been resolved and the clinical trial evidence is adequate to support registration it is not yet clear that the sponsor is able to market this product for all indications approved for the innovator adalimumab product (Humira). This is to be resolved outside the forum of the ACM.

Proposed action

The Delegate had no reason to say, at this time, that the application for Amgevita (adalimumab) should not be approved for registration.

Request for ACPM advice

The committee was requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The indications requested in the original submission for Amgevita remain unchanged. During review, Amgen added newly approved indications for Humira as suggested by the clinical evaluator. The indications requested for Amgevita therefore now also include hidradenitis suppurativa, uveitis and enthesis-related arthritis. The amended indications can be found in the annotated PI.

The Delegate has requested the ACM's advice on any issues it thinks may be relevant to a decision on whether or not to approve this application.

The marketing application for Amgevita presented comprehensive results of analytical similarity, nonclinical, and clinical studies to establish the biosimilarity of Amgevita to adalimumab (Humira). The Amgevita quality program demonstrated that Amgevita is analytically similar to both adalimumab (US) and adalimumab (EU), thereby supporting use of clinical data generated using adalimumab sourced from both regions. Minor analytical differences in biological attributes observed between Amgevita and the reference product were shown not to impact biological activity, mechanism of action, or PK. The results of these studies comprehensively demonstrated the biosimilarity of Amgevita to adalimumab.

Following the establishment of analytical similarity of Amgevita to adalimumab, clinical equivalence of Amgevita versus adalimumab in efficacy, safety and immunogenicity was confirmed in two independent clinical trials (Study 20120262 and Study 20120263). These trials were conducted in rheumatoid arthritis and plaque psoriasis subjects respectively. The results presented confirmed the clinical equivalence of Amgevita and adalimumab, and combined with the analytical, nonclinical and PK similarity data, contributed to the evidence to establish the biosimilarity of Amgevita to adalimumab.

The Delegate has noted the following issue:

> *'While quality issues have been resolved and the clinical trial evidence is adequate to support registration it is not yet clear that the sponsor is able to market this product for all indications approved for the innovator adalimumab product (Humira). This is to be resolved outside the forum of the ACM'.*

The TGA have adopted EU Guideline EMEA/CHMP/BMWP/42832/2005: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues. This guideline states the following in relation to extrapolation of indications:

'*In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications. Possible safety issues in different subpopulations should also be addressed*.'

The marketing application for Amgevita presented data from two global clinical studies in rheumatoid arthritis and plaque psoriasis, as discussed above. The Amgevita indications proposed for registration in Australia include all those approved for the innovator product Humira:

- rheumatoid arthritis
- plaque psoriasis
- polyarticular juvenile idiopathic arthritis
- ankylosing spondylosis
- Crohn's disease in adults and children ≥6 years
- ulcerative colitis
- psoriasis
- uveitis
- hidradenitis suppurativa
- enthesis-related arthritis.

The clinical trial data presented for Amgevita established clinical equivalence of ABP 501 to adalimumab in the indications studied. The results '*convincingly demonstrated clinical equivalence for subjects with rheumatoid arthritis and subjects with plaque psoriasis*' (Delegate's Overview above). Furthermore, the indications that Amgen selected to study in clinical trials were suitable to allow extrapolation across other Humira indications, as supported by the clinical evaluator's comment '*The sponsor has chosen two appropriate clinical study populations (indications) to enable extrapolation to the other approved indications for the reference product*'.

Extrapolation is based upon the premise that a biosimilar product that has been demonstrated to be highly similar to the reference product through multiple lines of testing, especially those known to be important to the mechanism of action in each indication, is expected to have similar clinical activity in all indications for which the reference product has been tested and approved. Therefore, the findings of no meaningful analytical, nonclinical, or clinical differences between ABP 501 and adalimumab support extrapolation to the full range of indications for which adalimumab is approved. This position is reinforced by the clinical evaluators comment '*extrapolation to all currently approved indications of the reference product is supported from a clinical evaluation point of view*' and also by the clinical evaluator's proposal to incorporate a newly approved Humira indication (hidradenitis suppurativa) during review. Subsequently, the sponsor proposed inclusion of a further newly registered Humira indication (enthesis-related arthritis) which was accepted. Amgen therefore agrees with the clinical evaluator and Delegate's

opinion that the extrapolation of therapeutic similarity shown in the two indications studied with Amgevita to all other approved indications for Humira is appropriate.

The Delegate has recommended several revisions to the Amgevita Product Information. These revisions have all been incorporated into the draft PI provided with this response.

Advisory committee considerations

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Amgevita pre-filled syringe pen injector containing 20 mg/0.4 mL, 40 mg/0.8 mL, 40 mg/0.8 mL of adalimumab to have an overall positive benefit-risk profile for the indications as per the innovator product Humira:

- *rheumatoid arthritis;*
- *polyarticular juvenile idiopathic arthritis;*
- *psoriatic arthritis;*
- *ankylosing spondylitis;*
- *Crohn's disease in adults and children (≥ 6 years);*
- *ulcerative colitis;*
- *psoriasis;*
- *hidradenitis suppurativa (added during evaluation);*
- *uveitis (added during evaluation); and*
- *enthesitis-related arthritis (era).*

In making this recommendation the ACM:

- noted this is the first application in Australia for a biosimilar version for adalimumab
- noted the number of extrapolated indications to consider
- expressed concern that multiple switching of biosimilar products would be an issue in the future.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

- The ACM noted that the only quality use of medicine issue will be the potential difference in injection device in the context of switching between biosimilar medicines.
- The ACM agreed that the data provided supports the listing of Amgevita for the proposed indications.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Amgevita adalimumab (rch) 40 mg/0.8 mL injection solution syringe within a pen injector and Amgevita adalimumab (rch) 40 mg/0.8 mL injection solution syringe Amgevita adalimumab (rch) 20 mg/0.4 mL injection solution syringe, indicated for:

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.

Juvenile idiopathic arthritis

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

Enthesitis-related arthritis

Amgevita is indicated for the treatment of enthesitis-related arthritis in children, who have had an inadequate response to, or who are intolerant to, conventional therapy.

Psoriatic arthritis

Amgevita is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderately 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 in adults and children

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

and adolescent patients from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and 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

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.

Specific conditions of registration applying to these goods

1. The EU- Risk Management Plan (EU-RMP), version 1.2, dated November 2016, data lock point 8 May 2015, with Australian specific annex (version 3.0, dated 14 February 2017), and any subsequent revisions, as agreed with the TGA will be implemented in Australia as a condition of registration.
2. Batch Release Testing & Compliance with Certified Product Details (CPD):

   It is a condition of registration that all batches of Amgevita™ adalimumab (rch) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

   It is a condition of registration that each batch of Amgevita™ adalimumab (rch) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.
3. It is a specific condition of registration for Amgevita that the Product Information and Consumer Medicine Information documents be updated within ONE month of safety-related changes made by the innovator. It is your responsibility to routinely check the TGA website at www.ebs.tga.gov.au for any updates to the innovator Product Information.

Attachment 1. Product Information

The PI for Amgevita approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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