Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Adalimumab

Proprietary Product Name: Hadlima

Sponsor: Samsung Bioepis AU Pty Ltd

March 2019

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

Common abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody dependent cell mediated cytotoxicity
AE	Adverse event
AID	Auto injector device
AS	Ankylosing spondylitis
AUC_{inf}	Area under concentration-time curve from time zero to infinity
AUC_{last}	AUC-time curve from time zero to last detectable drug concentration
BMI	Body mass index
CDC	Complement dependent cytotoxicity
CL/F	Apparent drug clearance
CI	Confidence interval
C_{max}	Maximum serum concentration
CRP	C-reactive protein
CV	Coefficient of variation
DAS	Disease activity score
DMARD	Disease modifying anti-rheumatic drug
ECG	Electrocardiograph
ESR	Erythrocyte sedimentation ratio
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full analysis set
GCP	Good clinical practice
GLP	Good laboratory practice

Abbreviation	Meaning
GOF	N-linked glycosylation lacking terminal galactose residues (G0), but is fucosylated (F)
HS	Hidradenitis suppurativa
IL-8	Interleukin 8
ISR	Injection site reaction
IV	Intravenous
JIA	Juvenile idiopathic arthritis
LS	Least squares
MHRD	Maximum human recommended dose
mTSS	Modified total sharp score
MTX	Methotrexate
NAb	Neutralising antibodies
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PPS	Per protocol set
PsA	Psoriatic arthritis
PSOR	Plaque psoriasis
PT	Preferred term
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SB5	Hadlima adalimumab drug development code
SC	Subcutaneous
SOC	System Organ Class

Abbreviation	Meaning
TB	Tuberculosis
T_{max}	Time to maximum drug concentration
TNF	Tumour necrosis factor
TNF α	Tumour necrosis factor alpha
TNF β	Tumour necrosis factor beta; lymphotoxin
Tg197	Transgenic mouse model of polyarthritis
UC	Ulcerative colitis
ULN	Upper limit of normal
VCAM-1	Vascular cell adhesion molecule 1

I. Introduction to product submission

Submission details

Type of submission:	New biosimilar medicine
Decision:	Approved
Date of decision:	18 January 2018
Date of entry onto ARTG:	24 January 2018
ARTG numbers:	284248, 284249
Active ingredient:	Adalimumab
Product name:	Hadlima
Sponsor's name and address:	Samsung Bioepis AU Pty Ltd Level 16/ 201 Elizabeth St Sydney NSW 2000
Dose form:	Solution for injection
Strength:	40 mg
Containers:	Pre-filled syringe; pre-filled syringe with autoinjector
Pack size:	2
Approved therapeutic use:	*Rheumatoid Arthritis* *Hadlima 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.* *Hadlima can be used alone or in combination with methotrexate.*
Route of administration:	Subcutaneous
Dosage:	The recommended dose of Hadlima for adult patients with rheumatoid arthritis is 40 mg administered fortnightly as a single dose. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics may be continued during treatment with Hadlima. Some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of Hadlima to 40 mg every week.

Product background

This AusPAR describes the application by Samsung Bioepis Pty Ltd (the sponsor) to register the biosimilar medicine Hadlima adalimumab 40 mg solution for injection in either a PushTouch auto injector or a pre filled syringe for the following indications:[1]

Rheumatoid Arthritis

> *Hadlima 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.*
>
> *Hadlima can be used alone or in combination with methotrexate.*

Juvenile Idiopathic Arthritis

> *Polyarticular Juvenile Idiopathic Arthritis*
>
> *Hadlima 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* ***and ≥ 30 kg body weight*** *who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Hadlima can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.*
>
> *Enthesitis-Related Arthritis*
>
> *Hadlima 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

> *Hadlima 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

> *Hadlima is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.*

Crohn's Disease in Adults and Children ***in severe CD*** *≥ 6 years* ***and ≥ 40 kg body weight***

> *Hadlima is indicated for the treatment of moderate to severe Crohn's disease* ***in adult and severe Crohn's disease in children, ≥ 6 years of age and ≥ 40 kg body weight,*** *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 to infliximab.*

Ulcerative Colitis

> *Hadlima 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).*

[1] Please note that during the course of this submission the requested indications were revised.

Psoriasis in Adults and Children

> *Hadlima is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.*
>
> *Hadlima is indicated for the treatment of severe chronic plaque psoriasis in children and adolescent patients from 4 years of age* ***and ≥ 40 kg body weight*** *who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.*

Hidradenitis Suppurativa

> *Hadlima 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

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

The proposed treatment indications for Hadlima are similar, but not identical, to the registered treatment indications for the reference product, Humira. The text highlighted in bold shows the additional proposed elements for Hadlima that do not appear in the Humira treatment indication wording.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences that bind with high affinity and specificity to soluble human tumour necrosis factor (TNF) alpha (TNF α), but not lymphotoxin (tumour necrosis factor beta (TNF β)), thereby preventing the interaction between TNF, and the p55 and p75 cell surface TNF receptors. As a consequence, TNF is rendered biologically inactive.

The submission proposes registration of the following strengths and dosage forms of Hadlima: 40 mg of adalimumab dissolved in 0.8 mL sterile solution, presented in single use, pre-filled syringes (PFS) and as an auto-injector device (AID).

The reference product, Humira has 3 dose presentations currently registered in Australia: 10 mg/0.2 mL and 20 mg/0.4 mL (both for paediatric use only; only available as pre filled syringe (PFS)) as well as the 40 mg/0.8 mL presentation (for adult and paediatric use; presented as PFS and auto injector device (AID)). The 10 mg vial presentation of Humira is not currently marketed in Australia.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) 24 January 2018.

At the time the TGA considered this submission, Hadlima was approved in the European Union (EU) via the centralised procedure (August 2017), and in the Republic of Korea (September 2017). A submission was also under consideration in Canada.[2]

[2] The submission in Canada was approved in May 2018 after the registration in Australia.

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 time line

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Time line for submission PM-2016-03547-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	3 January 2017
First round evaluation completed	31 May 2017
Sponsor provides responses on questions raised in first round evaluation	31 July 2017
Second round evaluation completed	5 October 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	31 October 2017
Sponsor's pre-Advisory Committee response	14 November 2017
Advisory Committee meeting	30 November to 1 December 2017
Registration decision (Outcome)	18 January 2018
Completion of administrative activities and registration on ARTG	24 January 2018
Number of working days from submission dossier acceptance to registration decision*	214

*Statutory time frame is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Introduction

Hadlima (also referred to as SB5) adalimumab has been developed as a similar biological medicinal product to the reference innovator product Humira. Hadlima drug product (DP) is a clear to opalescent, colourless to pale brown, sterile and preservative free solution for

injection. Hadlima is presented as a single use PFS and a single use AID containing 40 mg of adalimumab to be administered via subcutaneous (SC) injection. Humira was first approved in 2002 by the United States (US) Food and Drug Administration (FDA), in 2003 by the European Commission (EC), and in 2003 by the Therapeutic Goods Administration (TGA).

Hadlima adalimumab is a fully human monoclonal antibody (mAb) composed of two IgG1 heavy chains and two kappa light chains. Adalimumab binds specifically to TNFα and neutralises the biological function of TNFα by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.

Humira has been widely used in clinical practice for about 13 years, with a well characterised pharmacological, efficacy, and safety profile. Originally, Humira was approved for use in moderate to severe rheumatoid arthritis, and indications have been extended to include the use in treatment of patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), psoriatic arthritis, ankylosing spondylitis, Crohn's disease in adults and children, ulcerative colitis, psoriasis in adult and children, hidradenitis suppurativa, and uveitis. The sponsor claims the same therapeutic indications for the proposed biosimilar Hadlima as granted for Humira in Australia. However, as Hadlima is currently only available as a 40 mg PFS and AI presentations, the sponsor intends to claim the paediatric indications only for those patients who can administer the full 40 mg dose.

Drug substance (active ingredient)

Hadlima is a homodimer of a chimeric protein, which consists of 1,330 amino acids, 665 amino acids for each chain. The homodimer has a molecular weight (MW) of approximately 148 kDa.

Full details of the elucidation of primary, secondary, tertiary or quaternary structure are detailed in the dossier.

Physical and chemical properties

- Appearance Clear to opalescent and colourless to pale brown solution
- Molecular Weight of approximately 148 kDa
- [information redacted]
- Glycosylation One N-linked glycosylation site is located at Asn301 on each heavy chain and there are no O-linked glycosylation sites.
- Biological activity; adalimumab binds specifically to TNFα and neutralises the biological function by blocking its interaction with the p55 and p75 cell surface TNFα receptors. Adalimumab also modulates biological responses that are induced or regulated by TNFα, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1 and ICAM-1).

Manufacture/Manufacturer(s)/GMP status

The manufacturing process involves cell culture expansion, a production bioreactor, harvest of the cell culture fluid, purification, and dispensing, resulting in highly purified Hadlima DS.

The purification process has been designed to isolate Hadlima from process components, host cell DNA, and host cell proteins. Additionally, the process is designed to provide clearance or inactivate model adventitious viruses in scale-down studies. A detailed description of the purification process manufacturing steps was provided.

The PFS manufacturing process involves thawing, pooling, and mixing of the drug substance, followed by sterile filtration and aseptic syringe filling, and plunger placement. The PFS is then assembled with the corresponding secondary packaging components into either PFS or AID.

All manufacturing steps are validated. There were several manufacturing sites still awaiting clearance from TGA.[3]

Specifications

All analytical procedures are validated. There are no issues pertaining to specifications.

Drug product

Stability

Based on all the data submitted the quality evaluator recommended the following shelf life conditions:

- 36 months when stored at 5 ± 3°C, protect from light.
- In use: 2 weeks at room temperature condition below 25°C. Once removed from the refrigerator for storage, the syringe must be used within 14 days or discarded, even if it is returned to the refrigerator.

Biopharmaceutics

Bioavailability/bioequivalence data are not required.

Biosimilarity

The active substance of Hadlima adalimumab (rch) has been developed as a similar biological medicinal product (biosimilar) to that of the currently registered reference product Humira.

During the development of Hadlima, Humira from EU was used as the main reference product to demonstrate biosimilarity in terms of quality and non-clinical comparability exercise. Additional bridging comparability study was performed between the EU Humira and Australian Humira to present EU Humira as representative of the Australian registered product (Australian Humira).

Extensive characterisation studies involving comparison of primary, secondary and tertiary structures, physicochemical properties and biological activities showed that Hadlima and EU Humira are generally similar. However, several differences have been noted as highlighted below:

- Carbohydrate Structure; % Afucose and % G0F;[4]

[3] At the time of approval all required GMP clearances were in place.

- % Afucose level of Hadlima was slightly higher than that of the upper limit of the similarity range;
- % G0F levels of Hadlima were found to fall below the similarity range.

The minor differences in % Afucose and % G0F between Hadlima and Humira were shown to have no effect on the FcγRIIIa binding and antibody dependent cell mediated cytotoxicity (ADCC) activities of the drug product. Furthermore, all other glycan structure were shown to be in the similar range, therefore the differences were considered not significant.

- Purity and impurities
  - % main of Hadlima batches were out of similarity range, which was attributed to the higher % non-glycosylated heavy chain level of Hadlima than that of EU Humira. The N-glycosylation at Fc region of antibodies is known to be associated with Fc related functional activities.

The slight differences observed were not considered to have an impact on the biological activity. Therefore, the differences in %Main of Hadlima and EU Humira were not considered significant.

- Charge variants
  - The relative contents of acidic variants in Hadlima were higher than the similarity range, whereas the relative content of the basic peak of Hadlima was lower than the similarity range.

In order to identify the possible causes and rule out the residual uncertainty on the difference in the charged profiles of Hadlima and Humira, the nature of the molecular forms of the acidic, main and basic regions were elucidated. However, no differences in the molecular forms were observed in the charge variants of Hadlima and EU Humira. Furthermore, to evaluate the impact of the charge heterogeneities on biological activity, SAR studies were performed using CEX-HPLC fractionated peaks. It was found that the charge variant content did not affect biological activity including TNFα binding and ADCC.

The evaluator requested the sponsor to comment on the differences observed in charge variants with regards to inducing apoptosis. In response the sponsor has stated that the differences observed in charge variants should not result in differences in apoptotic activity for the following reasons:

1. The identified nature of the charge variants may primarily affect Fc related function, and apoptosis is induced through the Fab region of an antibody, the difference in charge variants is not likely to have an impact.
2. TNFα binding activity is similar between Hadlima and Humira across all the fractionated charge variants, therefore, it implies that apoptosis activities in all fractionated charge variants will be similar.
3. Tertiary structure analysis revealed no difference between Hadlima and Humira despite the observed difference on charge variants.

The detailed analysis provided by the sponsor in the response provided sufficient assurance that the observed differences in charge variants between Hadlima and EU Humira should not affect the apoptotic activity of Hadlima drug product.

Overall, the sponsor has demonstrated that Hadlima is comparable to Humira in terms of structure, species, function and degradation profile (that is, physicochemical and biological).

Quality summary and conclusions

There are no objections to the registration of this product from sterility, endotoxin, container safety and viral safety related aspects.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Hadlima have been controlled to an acceptable level.

With respect to quality matters the PI, Consumer Medicine Information (CMI) and labels are acceptable.

IV. Nonclinical findings

Introduction

Hadlima, which contains adalimumab, and is intended as a biosimilar to Humira. Hadlima is proposed to be used only for the rheumatoid arthritis indication of Humira (as revised in the response to first round questions). Dose, administration route and dosing frequency of Hadlima match those of Humira, as outlined in the approved Australian PI for Humira (Version 39; 19 May 2017).

General comments

The scope of the nonclinical testing program for Hadlima (drug development code: SB5) is in general accordance with guidance on nonclinical testing of similar biological medicinal products.[5] Data presented in the nonclinical module consisted of 2 in vivo studies: a comparative pharmacology study in a transgenic mouse model of polyarthritis (Tg197); and a 4 week repeat dose toxicity study in cynomolgus monkeys including toxicokinetic measurements.

In vitro comparability studies on the biological characteristics of SB5 against Humira will be evaluated and commented further by the quality evaluator. However, it is noted that the SB5 drug product and/or drug substance batches used in the nonclinical studies were not subject to any of these comparability assessments. In response to a question raised, the sponsor indicated that at the time nonclinical studies were conducted, the manufacturing stage was locked at [information redacted] production which preceded the in vitro bio comparability assessments reported. However, the sponsor referred to comparability assessments that were conducted on SB5 batches from earlier stages of the manufacturing development process. The batch used in nonclinical studies) and clinical batches showed comparable functional activities that were within the EU Humira similarity ranges. Therefore, based on this information, the SB5 drug product batch used in nonclinical studies is considered adequately represented in the main biosimilarity assessments.

Although EU sourced Humira was claimed to be the reference product in nonclinical and clinical studies, it was noted that nonclinical studies only used US sourced Humira as comparator. In their response to questions, the sponsor explained that because the comparability assessments showed similarity between the tested batches of US and EU Humira, it can be inferred that other US Humira lots not part of the comparability assessment are also comparable to EU sourced Humira. To further support this claim, the sponsor presented a tabular summary outlining some physicochemical characteristics of

[5] Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues: EMA/CHMP/BMWP/403543/2010

the US Humira lot used in nonclinical studies that showed they were within the EU Humira similarity range. This rationale is considered acceptable.

Pharmacology

Adalimumab is a human recombinant monoclonal antibody directed against human TNFα and confers anti-inflammatory activity by preventing the binding of soluble and membrane TNFα to TNF receptors. The Fc fragment also contributes to the biological activity of adalimumab. Biosimilar adalimumab SB5 would be expected to display the same pharmacological actions as innovator Humira.

In vitro comparability studies between SB5 (as clinical and product validation run batches) and EU, US and Korean sourced Humira showed a number of qualitative similarities in biological activity. Criteria for establishing biosimilarity were based on whether the tested batches fell within similarity range values that were derived from statistical data on approximately [information redacted] batches of EU-sourced Humira. Further comment on the acceptability of these comparative assessments will be provided by the quality evaluator. The affinity of SB5 for soluble and transmembrane TNFα, TNFα neutralisation, anti-apoptotic actions, anti-transmembrane TNFα (anti-tmTNFα) mediated induction of apoptosis, inhibition of interleukin 8 (IL-8) release, induction of regulatory macrophages, enhanced soluble vascular cell adhesion molecule 1 (VCAM-1) expression, T cell anti-proliferation activity, Fc gamma receptor binding and related functions (ADCC and complement dependent cytotoxicity (CDC) activity) were all comparable to EU, US and Korean sourced Humira. As well, like all three Humira comparators, SB5 also did not bind to TNFβ/lymphotoxin.

In vivo demonstration of comparative efficacy of SB5 to Humira (0.5, 3 and 10 mg/kg) was shown in a transgenic mouse model of polyarthritis (Tg197), which develops human TNFα-induced polyarthritis by 6 to 7 weeks of age and is an accepted animal model for human arthritis. Three week old mice received twice weekly intraperitoneal injections of adalimumab or vehicle up to Week 10. Indicators of efficacy were based on in-life observations (improvements to body weight and arthritis scores) and post mortem examination of limb joints (histopathology scores). Relative to vehicle control group findings, body weight increases and reductions in arthritis scores (indicative of reduced severity of disease) were similar in both SB5 and Humira groups. Improvements in histopathology scores were also similar and were significantly different from vehicle controls at doses ≥ 3 mg/kg, whereas interdose comparisons between the two adalimumab groups did not find significant differences. Overall, in a mouse model of arthritis SB5 demonstrated anti-inflammatory activity that was comparable to that of US sourced Humira.

In the original submission the sponsor provided justifications to support extrapolation of data for the other indications of Humira, which were mainly based on findings from the in vitro comparability assessments. The sponsor has since requested to change the indications being sought for approval and only register it for rheumatoid arthritis. Because the in vivo pharmacology studies concerned the sought after indication and demonstrated adequate comparability between SB5 and US Humira (an acceptable comparator on the basis of additional information), from a nonclinical perspective there are no specific concerns about adequate demonstration of comparable efficacies.

Pharmacokinetics

Comparative pharmacokinetic parameters were determined from toxicokinetic measurements ascertained from the 4 week repeat dose toxicity study in cynomolgus monkeys. Although there were slight differences in time to maximum plasma-drug

concentration (T_{max}) values in SB5 treated females compared with US Humira, overall, there were no significant or meaningful differences in pharmacokinetic parameters observed between SB5 and US Humira in cynomolgus monkeys following SC dosing at equivalent doses (32 mg/kg).

Bioequivalence in humans was claimed based on assessments made in healthy subjects who received single doses of SB5/Hadlima, EU Humira or US Humira.

Toxicology

The sponsor submitted a Good Laboratory Practice (GLP) compliant, 28 day comparative repeat dose toxicity study on SB5/Hadlima in cynomolgus monkeys. The study design was acceptable and consistent with guidelines on toxicity testing for biological medicines.[6] The dose utilised (32 mg/kg) was chosen because it was stated to be over 10 times higher than the maximum recommended human dose (MRHD) and dosing frequency was higher (weekly compared with fortnightly for most indications). They also referenced the original assessment of adalimumab/ Humira where chronic dosing of up to 215 mg/kg, intravenous (IV) for 39 weeks did not result in any dose limiting or other targeted toxicities. It should be noted that the guideline on biosimilar products[7] does not explicitly require toxicity testing if the in vitro comparability studies are acceptable; that is, that the biological activity and physicochemical attributes of the biosimilar and innovator are sufficiently similar. Although the quality evaluator will comment specifically on whether the comparability assessments are satisfactory, outwardly the summarised data on the biological activity of SB5 indicate comparable actions relative to EU, US and Korean sourced Humira, where measurements with SB5 for most tests fell within specified acceptance ranges.

In the toxicity study, a single dose of adalimumab was selected (32 mg/kg/week) and administered using the clinical route subcutaneous (SC); although, the dosing regimen differed slightly since adalimumab is generally given to patients on a fortnightly basis. Toxicokinetic parameters were also determined, and serum samples were analysed for the presence of anti-drug antibodies (ADA) against adalimumab. The toxicokinetic assessments, as summarised earlier, indicated comparable pharmacokinetic parameters between SB5/Hadlima and US Humira. The study did not find evidence of ADAs against adalimumab but it was speculated that high circulating levels of adalimumab may have masked their detection.

There were no mortalities in any of the groups, nor were there notable treatment related changes in clinical signs above sporadic and transient changes (sparse hair on hind limbs, skin scabbing and reddening, and watery faeces), which were seen in all groups including vehicle treated animals. Other parameters (body weight gain, ophthalmological, electrocardiograph (ECG), haematological, urinalysis and clinical chemistry parameters) were unchanged by either type of adalimumab treatment, and post mortem analyses did not reveal significant changes in either adalimumab group. There were no treatment related effects on organ weights in any of the groups. Infrequent injection site changes were reported which were of minimal to mild grade of severity (fibrosis, myofibre degeneration/regeneration, pigmented macrophages and mineralisation).

Overall, toxicity studies did not identify any unexpected toxicities with SB5 or any findings that were inconsistent to those with Humira. The nature, incidence and severity of findings with SB5 were generally comparable to those observed with US sourced Humira.

[6] EMA/CHMP/ICH/731268/1998 - ICH guideline S6 (R1) – Preclinical safety evaluation of biotechnology-derived pharmaceuticals.
[7] EMA/CHMP/BMWP/403543/2010 – Guideline on similar biological medicinal products containing monoclonal antibodies: nonclinical and clinical issues.

Pregnancy classification

The sponsor has proposed pregnancy category C.[8] This matches the existing category for Humira and is appropriate.

Comments on the nonclinical safety specification of the risk management plan

The results and conclusions drawn from the nonclinical program for SB5/Hadlima as detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat dose toxicity. The scope of the nonclinical program is in general accordance with the EMA guideline on nonclinical assessment of biological medicines (EMEA/CHMP/BMWP/42832/2005 Rev 1). Nonclinical in vivo studies only used US-sourced Humira, whereas the sponsor indicated that EU sourced Humira was the chief comparator.
- There were no significant differences between SB5/Hadlima and US sourced Humira in the in vivo comparative pharmacology, pharmacokinetic and toxicity studies.
- Based on the nonclinical studies submitted and additional information provided by the sponsor, all major concerns identified in the first round report have been resolved. Nonclinical demonstration of comparability between SB5 and innovator US Humira is considered acceptable and there are no nonclinical objections to registration.

The nonclinical evaluator also made comments relating to the draft PI but these are beyond the scope of the AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

This application is a full submission requesting the registration of a new chemical entity in Australia, Hadlima (also referred to as SB5), which is a biosimilar medicine of adalimumab. In this submission, similarity to Humira (that is, the reference medicinal product) is claimed. The application for Hadlima is requesting approval of the same 9 treatment indications currently approved for Humira in Australia,[9] which include active rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) in children and adolescents aged 2 to 17 years, psoriatic arthritis (PsA), chronic plaque psoriasis (PSOR) in adults and children (4 to 17 years), Crohn's disease (CD) in adults and children > 6 years of age, ulcerative colitis (UC), ankylosing spondylitis (AS), hidradenitis suppurativa (HS) and non-infectious uveitis.

[8] Pregnancy Category C is classified as 'Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.'
[9] This request was revised after the first round clinical evaluation to only include the RA indication.

The submission contains a single pivotal Phase III trial (Study SB5-G31-RA) with an active treatment period of 52 weeks, which primarily evaluated the comparative efficacy and safety of SB5 versus EU sourced Humira for the treatment of 544 adult subjects with active RA. The sponsor has also nominated the comparative pharmacokinetic (PK) and safety data provided by the Phase I trial (Study SB5-G11-NHV) as pivotal in this submission. Two additional clinical studies (SB5-G12-NHV and SB5-G21-RA) with open label designs were included in this submission, to mainly support the registration of the auto-injector device (AID) in addition to the pre-filled syringes (PFS).

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences that bind with high affinity and specificity to soluble human tumour necrosis (TNF-α), but not lymphotoxin (TNF-β), thereby preventing the interaction between TNF, and the p55 and p75 cell surface TNF receptors. As a consequence, TNF is rendered biologically inactive.

The submission proposes registration of Hadlima: 40 mg of adalimumab dissolved in 0.8 mL sterile solution, presented in single use, PFS and AID.

Humira has 3 dose presentations currently registered in Australia: 10 mg/0.2 mL and 20 mg/0.4 mL (both for paediatric use only; only available as PFS) as well as the 40 mg/0.8 mL presentation (for adult and paediatric use; presented as PFS and AID). The 10 mg vial presentation of Humira is not currently marketed in Australia.

Dosage and administration

Adalimumab is administered by subcutaneous (SC) injection. The proposed adult treatment indication for Hadlima has a recommended maintenance dose of 40 mg per fortnight.

Clinical rationale

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. It is the second most common form of arthritis and the most common autoimmune disease in Australia with a prevalence of 2%.

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease in children and is more common in females. The estimated prevalence of JIA in Australia is 1 in 1,000 children aged up to 16 years. Ankylosing Spondylitis (AS) affects approximately 0.5% of the population, mainly young to middle aged males. Plaque psoriasis (PSOR) is an inflammatory immune based skin disorder with a genetic disposition, occurring in 6 to 7% of the adult Australian population. Approximately 15% of all cases of PSOR begin in children before the age of 15 years, and the condition may start as young as infancy. About 25 to 30% of subjects with PSOR develop a concurrent inflammatory arthritis, psoriatic arthritis (PsA).

Hidradenitis Suppurativa (HS) is a chronic skin disorder, which usually occurs in the skin fold areas such as the axilla. The condition involves inflammatory nodules, cysts and abscesses and often has a substantial impact upon an affected individual's quality of life. The incidence and severity of autoimmune inflammatory bowel disease (Crohn's Disease (CD) and Ulcerative Colitis (UC)) have significantly increased in Australia in the last 3 decades with an estimated prevalence of 0.5% in 2013. It is estimated that up to 10 to 20% of all CD cases have an onset in paediatric years (< 17 years of age) at a mean age of 11 years. Non-infectious uveitis describes a broad range of inflammatory eye diseases characterised by swelling and redness of the eye, which if untreated can lead to loss of vision. They have a collective prevalence of up to 1%.

Current treatment options

The inflammatory arthritides are heterogeneous conditions in terms of clinical presentation, natural history and drug responsiveness. Published evidence and current international guidelines for the treatment of autoimmune inflammatory arthritis emphasise the importance of achieving clinical remission, or at least low disease activity, as both of these states are associated with a favourable long term prognosis. Conventional synthetic disease modifying drugs (in particular, methotrexate (MTX)), alone or in combination with each other, are the initial recommended treatments for most types of inflammatory arthritis apart from AS. Biological DMARDs, either as add-on or single drug therapy, is the next recommended line of therapy in active inflammatory arthritis after conventional synthetic DMARD failure or intolerability. While anti-TNF drugs and cytokine modulators have been shown to demonstrate significant efficacy in treating active inflammatory arthritis, a substantial proportion of patients are not achieving meaningful clinical responses.

Inflammatory bowel disease is typically treated with glucocorticoids (topical and/or systemic) in conjunction with immunosuppressant therapies such as azathioprine, 6-mercaptopurine and MTX. If insufficient response to these drugs occurs, then patients may be considered candidates for biological therapies such as anti-TNF medicines. Inflammatory skin disorders such as PSOR and HS are typically treated initially with topical glucocorticoids and if insufficient response is observed, then systemic therapies (such as MTX and retinoid) and/or phototherapy may be considered. Non-infectious uveitis is typically treated with topical or systemic glucocorticoids and/or Non-Steroidal Anti-Inflammatory Drug (NSAID).

TNF plays a central role in the molecular and cellular events occurring in the pathogenesis of several autoimmune inflammatory conditions. Elevated concentrations of TNF have been found in the synovium of those with active RA, PsA and AS, as well as in the skin lesions of PSOR. Elevated levels of TNF are found in the skin lesions of hidradenitis suppurativa (HS). Elevated TNF levels are found in the stool of patients with active inflammatory bowel disease and patients with non-infectious uveitis demonstrate up-regulated aqueous humour and serum levels of TNF. Anti-TNF medicines work by neutralising the activity of soluble TNF and preventing its binding to the 2 main TNF receptors (p55 and p75). These receptors are expressed on the membrane of monocytes and T lymphocytes, and circulate in the blood in soluble forms.

Adalimumab is a recombinant human monoclonal antibody, which inhibits the binding of TNF to the surface of cells expressing TNF receptors such as T lymphocytes in the synovium of patients with active RA. Humira is currently approved in Australia for use in 9 treatment indications. The central therapeutic effect of Humira in all these indications is mediated by TNF blockade. Reducing disease activity and slowing the progression of inflammatory disease are the key therapeutic goals in autoimmune disease with significant inflammatory characteristics. Adalimumab is well established and widely used in Australian adult and paediatric rheumatology, dermatology and gastroenterology clinical practice for > 15 years and has a well characterised benefit: risk profile.

Evaluator's commentary on the background information

Hadlima is the first biosimilar medicine of adalimumab proposed for registration in Australia. Two other anti-TNF medicines (infliximab and etanercept) already have biosimilar therapies approved in Australia, both of which have been granted the full list of treatment indications of the originator biologic medicine. Hadlima is available as a SC formulation and predominantly exerts its immunomodulatory effect via inhibition of soluble TNF, which is often elevated in various autoimmune disorders. In recent years, published evidence has supported a significant clinical practice change in treating

inflammatory autoimmune disease whereby tight and sustained control of disease activity is the desired outcome.

In general, the sponsor has adhered to the TGA guidelines on the registration of a biosimilar medicine in this submission. Moreover, the sponsor has provided information on the overseas regulatory status of Hadlima (that was pending registration applications in several contemporary jurisdictions). The sponsor has appropriately justified the formulation development program for Hadlima.

Some of the key issues to consider in this submission are common to biosimilar medicine applications. The sponsor needs to demonstrate that Hadlima results in clinical effects (efficacy and safety outcomes) that are comparable to the reference product, Humira. Furthermore, the biosimilar therapy needs to demonstrate equivalence with the reference drug for pharmacokinetic parameters as well as immunogenicity (mainly, rates and types of anti-drug antibody formation). However, lower rates of immunogenicity with the biosimilar may be acceptable.

Guidance

The TGA published guideline is called 'Evaluation of biosimilars' which was published on 30 July 2013 and was updated in December 2015.[10] This guideline notes that a biosimilar medicine is a version of an already registered biological medicine that:

1. Has a demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies
2. Before a biosimilar medicine can be registered in Australia, a number of laboratory and clinical studies need to be performed to demonstrate the comparability (biosimilarity) of the new biosimilar to the reference biological medicine already registered in Australia
3. The TGA has adopted a number of European guidelines that outline the quality, nonclinical and clinical data requirements specific to biosimilar medicines; and the ICH guideline on the assessment of comparability
4. For a biosimilar to be registered in Australia, the reference medicine must be a biological medicine that has been registered in Australia based on full quality, safety and efficacy data and the Australian reference medicine must have been marketed in Australia for a substantial period and have a volume of marketed use so that there is likely to be a substantial body of acceptable data regarding the safety and efficacy for the approved indications. However it may be possible for the sponsor to compare the biosimilar in certain clinical studies and in in vivo non-clinical studies to a medicine not registered in Australia in which case the reference medicine must be approved for general marketing by a regulatory authority with similar scientific and regulatory standards as the TGA (for example EMA or US FDA) and a bridging study must be provided to demonstrate that the comparability studies are relevant to the Australian reference medicine.
5. To justify extrapolated indications based on the adopted EU guideline.[11]
6. To have a clearly distinguishable tradename from all other products and the active ingredient is to use the same name as the reference's active ingredient without a specific biosimilar identifier suffix. The World Health Organization (WHO) are considering a naming convention for the active ingredients of all biological medicines, including biosimilars.

[10] https://www.tga.gov.au/publication/evaluation-biosimilars
[11] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

7. The inclusion of comparative clinical trial information in the PI along with a clear distinction of the clinical trial information generated on the reference medicine.
8. There may be post-registration requirements and biosimilars must have an RMP.

There are a number of specific clinical EU guidelines adopted by the TGA relevant to this submission, besides the general guidelines:

- CPMP/EWP/556/95 Rev 1: Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for Treatment of Rheumatoid Arthritis.
  Effective: 29 January 2007
- CHMP/437/04/Rev 1: Guideline on Similar Biological Medicinal Products.
  Effective: 25 May 2015
- EMA/CHMP/BMWP/86289/2010: Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. Effective: 1 June 2014
- EMA/CHMP/BMWP/403543/2010: Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues.
  Effective: 17 August 2015.

Contents of the clinical dossier

The clinical dossier contains a pivotal Phase I trial (Study SB5-G11-NHV) that aimed to compare the pharmacology, safety and tolerability of 3 different formulations of adalimumab (SB5, EU sourced Humira and US sourced Humira) and a single pivotal Phase III trial (Study SB5-G31-RA) in adult patients with active RA. The clinical program had the objective of achieving regulatory guidelines for the demonstration of biosimilarity between SB5 and the approved reference product, Humira. The clinical dossier also contained 2 additional trials (Studies SB5-G12-NHV and SB5-G21-RA) to support the approval of the AID administration device.

The submission contained the following clinical information:

- 1 pivotal clinical pharmacology study (Study SB5-G11-NHV) in healthy volunteers that provided pharmacokinetic (PK) data and supporting safety information.
- 1 supporting clinical pharmacology trial (Study SB5-G12-NHV) in healthy volunteers that provided PK data and safety information on a single 40 mg SC dose of SB5 given by either AID or PFS.
- No population PK analyses.
- 1 pivotal efficacy/safety study (SB5-G31-RA) in adult patients with active RA, which included a PK sub-study reporting exploratory steady-state PK data.
- No dose-finding studies.
- 1 supporting open label trial (Study SB5-G21-RA) of SB5 administered by PFS and AID in subjects with RA to demonstrate comparability in terms of injection site pain.

The submission also included; Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Biopharmaceutical Studies and associated Analytical Methods, Summary of Clinical Pharmacology Studies and literature references.

Paediatric data

The submission did not include any paediatric specific data.

Good clinical practice

All of the clinical studies provided in this submission for Hadlima were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Evaluator's commentary on the clinical dossier

The sponsor designed the clinical development program for Hadlima to demonstrate equivalent safety, efficacy and pharmacokinetics outcomes to the appropriate reference product, Humira. The submission includes 4 clinical trials including 1 pivotal randomised, multi-centre, double blind, Phase III Study SB5-G31-RA evaluating the comparative efficacy and safety of SB5 and EU sourced Humira in an active RA population setting. The Phase III trial added adalimumab (SB5 or Humira) to patients with an inadequate response to MTX. Additional Phase I studies were conducted to assess the safety and pharmacokinetic properties of SB5 to Humira as well as compare the administration of SB5 by 2 different administration devices in healthy volunteers. The submission also included the Phase II Study SB5-G21-RA in subjects with RA to further examine the usability and tolerability of SB5 given by AID or PFS. Clinical study reports were provided for each trial and the safety data was presented by individual study as integrated datasets were not appropriate. Overall, the data in the submission was well presented in a ready to use electronic format.

The clinical development program for Hadlima has 3 specific limitations that need to be considered. Firstly, RA is the only disease condition in which Hadlima has been studied, and careful reflection about the sensitivity of the efficacy measures in the RA studies is required. Secondly, no specific paediatric studies have been conducted by the sponsor. Finally, the dataset does not contain any information about multiple treatment switches between the adalimumab formulations. The pivotal RA Study SB5-G31-RA examined the effect of a single 1 way switch in therapy from Humira to Hadlima in a subgroup of patients.

Pharmacokinetics

In accordance with the relevant TGA adopted EU guidelines; [12,13] the clinical dossier presented a total of 3 studies for demonstrating similarity in PK characteristics between Hadlima and Humira. The clinical Phase I, single dose trial (Study SB5-G11-NHV) in young-middle aged, healthy volunteers was considered the primary PK study for demonstrating similarity, and the PK sub-study of the pivotal Phase III RA clinical trial (Study SB5-G31-RA) provides supporting evidence for PK similarity in a patient population. The third PK study included in this submission was a Phase I, single dose trial (Study SB5-G12-NHV) that compared the PK of Hadlima administered by PFS and AID in healthy volunteers. None of the studies had significant deficiencies that excluded their results from consideration.

Studies providing pharmacokinetic data

Pharmacokinetics in healthy subjects

- Study SB5-G11-NHV

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

- Study SB5-G12-NHV.

Pharmacokinetics in the target population

Study SB5-G31-RA was a Phase III clinical study that aimed to demonstrate that Hadlima was equivalent to EU sourced Humira (40 mg dose given once every 2 weeks by SC injection) in terms of efficacy and safety outcomes.

Evaluator's conclusions on pharmacokinetics

The PK characteristics of Hadlima and the approved reference product Humira (EU and US sourced) were investigated in 3 clinical trials. Study SB5-G11-NHV was specifically designed to evaluate the PK of Hadlima in healthy volunteers aged between 18 and 55 years, and to demonstrate the PK equivalence of Hadlima with Humira (EU and US sourced) for the co-primary endpoints of AUC_{inf};[14] and C_{max}.[15] These co-primary PK endpoints are appropriate for demonstrating PK similarity. It was agreed with the EMA and US FDA to determine PK equivalence using a single dose trial for which AUC_{inf} and C_{max} would lie within the pre-determined equivalence margin of 0.8 to 1.25. This was observed to be correct for Study SB5-G11–NHV, in which Hadlima was demonstrated to have geometric least squares (LS) means ratios compared to both EU and US sourced Humira close to 1 (and always within the 0.8 to 1.25 equivalence margin) for both primary PK endpoints. Study SB5-G11-NHV also demonstrated that Hadlima was bioequivalent with the appropriate reference products of Humira in terms of the key secondary PK parameters including AUC_{last};[16] T_{max} and $T_{½}$.

Study SB5-G31-RA demonstrated that Hadlima and EU sourced Humira achieve similar trough drug concentrations of adalimumab between Weeks 4 and 24. However, both formulations of adalimumab exhibited high inter patient variability in drug exposure with the coefficient of variation (CV)% for serum trough levels ranging from 51.1 to 68.4% for Hadlima and 45.8 to 68.9% for EU sourced Humira.

Study SB5-G12-NHV was the third study in this submission that collected PK data and its primary objective was to demonstrate the equivalence of Hadlima administered SC by AID and PFS. The trial enrolled a total of 190 healthy subjects (95 subjects in each arm) and all but 1 subject in the SB5 PFS treatment group received a single SC 40 mg dose of Hadlima. All assessed PK parameters including AUC_{inf}, C_{max} and T_{max} were comparable across the 2 treatment groups. This study specifically supports the PK equivalence of both administration devices for registration purposes.

All 3 of the studies showed mean serum concentration time profile data consistent with the known PK characteristics of adalimumab. In particular, adalimumab is slowly absorbed from the site of SC injection (mean T_{max} was 150 to 166 hours in Study SB5-G11-NHV and median T_{max} was 168 hours in Study SB5-G12-NHV) and slowly cleared with the mean $T_{½}$ ranging from 320 to 384 hours. Both studies that examined for anti-drug antibodies (ADA) to adalimumab showed a high incidence of it developing (> 95% of all subjects in Study SB5-G11-NHV and > 30% of subjects in Study SB5-G31-RA up to 24 weeks). In Study SB5-G11-NHV, the incidence of post dose neutralising antibodies (NAbs) was also high in each of the treatment groups with no statistically significant differences between the arms. In the SB5 group, 79.0% (49/62) of subjects had a positive result for NAb, which was numerically slightly lower than that reported for the 2 Humira groups (80.0% (48/60) for EU Humira and 82.5% (52/63) for US sourced Humira). The incidence of developing NAb at Week 52 in Study SB5-G31-RA was 52.5% (73/139). The higher incidences of post dose ADA and NAb development in Study SB5-G11-NHV versus

[14] AUC_{inf} : Area Under Concentration-Time curve from time zero to infinity
[15] C_{max} : Maximum serum concentration
[16] AUC_{last} : AUC-Time curve from time zero to last detectable drug concentration

SB5-G31-RA may be explained by the concomitant administration of low dose MTX in Study SB5-G31-RA as this has been associated with lower rates of immunogenicity. Expectedly, minimum drug concentration (C_{trough}) adalimumab values were lower in patients who developed ADA, particularly those with medium to high titres of ADA.

The clinical dossier for Hadlima contained PK assessments collected in healthy volunteers and a subset of 356 adult patients with active RA (that is 1 approved treatment indication of the use of Humira). Hence, it is unknown whether or not there any significant PK differences between Humira and Hadlima exist for the other claimed treatment indications in adults (such as AS, PsA and PSOR), although it would seem unlikely. The sponsor has provided evidence from a literature review that the concurrent use of MTX reduces adalimumab clearance by approximately 40%. All enrolled patients in Study SB5-G31-RA were taking concomitant weekly low oral MTX with adalimumab, while none of the healthy volunteer subjects in Studies SB5-G11-NHV and SB5-G12-NHV were taking concomitant immunosuppression. However, there has been no clinical study with Hadlima in diseased individuals (for example adult subjects with PSOR, AS or inflammatory bowel disease) where the concurrent use of MTX is typically not part of the treatment strategy with adalimumab. It is unknown whether the PK and immunogenicity profile (anti-drug antibody status) of Hadlima in those other adult treatment patients may be significantly altered without the concurrent use of MTX. Furthermore, no PK data has been obtained in children and the sponsor is requesting consideration of the approved paediatric treatment indications for adalimumab across a very broad age range (2 to 17 years).

Overall, the PK assessments provided in this submission for the registration of Hadlima as a biosimilar product of Humira are appropriate and the data largely meets the minimum criteria of supporting evidence for PK bioequivalence.

Pharmacodynamics

Studies providing pharmacodynamic data

This submission did not contain any specific pharmacodynamic (PD) data for Hadlima collected in the clinical studies. The sponsor states that the PD effects of adalimumab have been well characterised in the published Humira trials and registration process. Furthermore, the sponsor asserts that in vitro and in vivo non-clinical studies provided in this submission demonstrate similarity between Hadlima and Humira in anti-TNF mediated PD effects.

As a proposed biosimilar of Humira, the applicant states that no further PD studies of Hadlima are required by the relevant regulatory guidelines [12,13] and that clinical evidence for comparability can be demonstrated by PD surrogate endpoints or clinical evidence. In the case of Hadlima, clinical evidence for similarity was to be demonstrated by clinical rather than PD endpoints. In patients with active RA, acute phase reactants of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation ratio (ESR) can be useful PD markers. Both CRP and ESR are sensitive indicators of the inflammatory activity of RA, and their measurement is included among the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria for improvement in RA.

Evaluator's conclusions on pharmacodynamics

In summary, the sponsor has not submitted any clinically derived PD data in this submission apart from the change in serum inflammatory markers (ESR and CRP) over time in the pivotal clinical Phase III study (SB5-G31-RA). This data will be presented in the clinical efficacy section of this report and in general shows there was similarity of PD

effect (for serum inflammatory markers) between the 2 formulations of adalimumab in an adult RA treatment population.

The applicant has also provided in vitro studies examining binding and cell based assays, as well as additional biological properties.(such as [information redacted]) to support similarity in the PD activity of Hadlima compared to Humira.

Dosage selection for the pivotal studies

The dose and regimen of adalimumab selected for the pivotal and supporting studies was based on the doses used in the Humira registration trials. This is an appropriate rationale for a biosimilarity submission.

In the pivotal study involving adult patients with active RA (Study SB5-G31-RA), adalimumab 40 mg injections were given fortnightly by SC injection. Adalimumab was co-administered with oral MTX 10 to 25 mg/week and folic acid (at least 5 mg/week). In addition, nearly half of the enrolled subjects were taking concurrent low dose oral corticosteroid therapy during the study and about one third took NSAID. In Study SB5-G31-RA, no loading dose of adalimumab was utilised, which is consistent with clinical practice and the current approved posology for Humira. The reference drug (Humira) used in the pivotal Phase III Study SB5-G31-RA was sourced from within the EU. Australian sourced Humira has been compared with EU Humira with respect to quality attributes and based on this analysis, the sponsor asserts that the comparability of Australian sourced Humira and EU Humira has been demonstrated, and therefore it is justifiable to use EU Humira as the nominated reference product. In this submission, the sponsor provided a bridging comparability study between 3 batches of Australian Humira and 1 batch of EU Humira, and concluded that their physicochemical and biological properties were within pre-defined similarity ranges. The opinion of the nonclinical evaluator with respect to the comparability of Australian and EU sourced Humira for quality attributes will be crucial to claim of justification.

In the supporting Phase I clinical studies (SB5-G11-NHV and SB5-G12-NHV), which evaluated healthy volunteers aged between 18 and 55 years, the investigated dose of adalimumab was 40 mg by SC injection on 1 occasion. No concomitant background therapy was allowed, which is appropriate for this type of study.

Efficacy

Studies providing efficacy data

The submission contains a single pivotal Phase III trial (Study SB5-G31-RA) in adult patients with active RA. For supportive purposes, the sponsor has also included an open label, Phase II study (SB5-G21-RA) that assessed and compared the usability of Hadlima administered SC by AID or PFS in 49 biologic DMARD naïve patients with RA. In the submission, the sponsor provided a literature review and analysis.

Evaluator's conclusions on efficacy

The clinical Phase III Study SB5-G31-RA demonstrated equivalent efficacy between Hadlima (SB5) and the reference product (EU sourced Humira) in adult patients with moderately to severely RA despite prior MTX, with the following outcomes being observed:

- ACR20 response rates at Week 24 for SB5 and EU Humira in PPS1 cohort were equivalent with the 95% confidence interval (CI) of the adjusted difference in ACR20

response rate between SB5 and Humira being −7.83% to 8.13%, which was contained within the predefined equivalence margin of −15% to 15%. This result was also replicated in the Full Analysis Set (FAS) and supported by the equivalence of the time response curve

- Secondary efficacy endpoints at Week 24 (including ACR50 and ACR70 response rates, ACR-N, AUC of ACR-N, mean change from baseline in DAS28 scores,[17] EULAR response and the AUC of the change in DAS28 from baseline up to Week 24) were similar between the SB5 and Humira arms; and
- Secondary efficacy endpoints assessed at Week 52 (such as ACR20, ACR50, and ACR70 response, major clinical response and mean change from baseline in modified Total Sharp Score (mTSS)) were also comparable between the SB5 and Humira groups (including between the Humira to SB5 switch and continuous Humira treatment groups).

In addition, Study SB5-G21-RA met its primary and secondary usability endpoint objectives by demonstrating that the injection site pain score (primary) and overall impression (secondary) for SC administration of SB5 at Week 2 for the PFS was equivalent to the AID pen at Week 6.

The sponsor has provided substantial evidence from non-clinical studies (not assessed as part of this report) that show similarity in structure for Hadlima compared to Humira, as well as the comparable binding of Hadlima and Humira to soluble and transmembrane TNF. In conjunction with the bioequivalence data from the PK studies, the efficacy data observed in patients with RA (Study SB5-G31-RA) provides evidence to suggest similar responses for SB5 and Humira in medical conditions that share common mechanisms of pathology to RA.

Safety

Studies providing safety data

In this submission, there was only 1 pivotal efficacy trial (Study SB5-G31-RA), which collected the following safety data:

- Adverse events (AEs) in general were assessed by completion of the AE Case Report Form (CRF) and physical examination performed at Weeks 2 and 4, every 4 weeks between Weeks 4 and 16, and every 8 weeks between Weeks 24 and 52, with an additional post-treatment follow-up visit at Week 60.
- AEs of particular interest, including serious infection, tuberculosis (TB) and injection site reactions (ISRs) were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests, including haematology (central lab), clinical chemistry (central lab) and urinalysis (local), were performed at baseline, Weeks 2 and 4, every 4 weeks between Weeks 4 and 16 and then every 8 weeks up until Week 52.
- Screening tests for TB (chest X-ray and QuantiFERON Gold testing) were routinely taken at baseline, and were performed again if TB was suspected thereafter.
- Vital signs such as blood pressure, heart rate and temperature were performed at each scheduled study visit. Complete physical examination was performed at screening

[17] DAS28 scores; Disease activity score and DAS28 is a measure of the activity of rheumatoid arthritis. The DAS is based upon treatment decisions of rheumatologists in daily clinical practice.

(including subject weight) and was abbreviated at subsequent visits (discretion of the site investigator).

- 12-lead ECG for central reading was taken at baseline and thereafter as required by clinical indication up to Week 52.
- Urine pregnancy testing was performed at baseline and every 4 weeks thereafter in women of reproductive age.
- Serum for anti-drug antibodies (ADA) to adalimumab was collected at baseline, as well as Weeks 4, 8, 16, 24, 32, 40 and 52. Analysis occurred via central laboratory.
- Serum for anti-nuclear antibodies and anti-dsDNA antibodies was collected at baseline, as well as Weeks 8, 24 and 52. Analysis occurred via central laboratory.

Patient exposure

In Study SB5-G31-RA, 99.4% (541/544) of subjects received at least 1 injection of SB5 or Humira (3 patients in the SB5 group did not receive injectable study drug). Patients who received at least 1 dose of investigational drug during Study SB5-G31-RA were included in the main safety analysis set, which was known as the Safety Set 1 (SAF1) cohort. Up to Week 24, the mean duration of drug exposure was similar at 150.7 days in the SB5 group and 148.7 days in the Humira arm; refer to Table 3.

The Safety Set 2 (SAF2) was the other safety analysis population evaluated in this trial and consisted of all SAF1 subjects who received at least 1 dose of investigational drug after re-randomisation at Week 24. The SAF2 cohort consisted of a total of 506 subjects (93.0% of 544 subjects in the Randomised Set), which included 254 (93.7% of 271) subjects in the original randomised SB5 group and 252 (92.3% of 273) subjects in the overall Humira arm (100% (125/125) of subjects in the Humira to SB5 treatment switch group at Week 24 and 98.4% (127/129) of subjects in the continued Humira arm). Up to Week 52, the mean duration of drug exposure was comparable at 333.6 days in the SB5 group and 324.6 days in the overall Humira arm (343.3 days in the Humira to SB5 switch group and 348.3 days in the continued Humira arm); refer to Table 3. The majority of continuing subjects (88.6 to 92.5%) in both treatment groups received all doses of study treatment up to Day 281 (that is > 9 months in Study SB5-G31-RA) resulting in a similar cumulative exposure to adalimumab for both treatment arms.

Table 3: Duration of exposure to adalimumab in Study SB5-G31-RA (SAF1 Cohort)

Duration of exposure (days)	SB5 40 mg	Humira® 40 mg			Total
		Overall	SB5 40mg	Humira® 40 mg	
	N=268	N=273	N=125[a]	N=127[a]	N=541
Summary statistics up to Week 24					
n	268	273			541
Mean	150.7	148.7			149.7
(SD)	(22.32)	(27.98)			(25.33)
Min, Max	1, 165	1, 166			1, 166
Summary statistics up to Week 52					
n	268	273	125	127	541
Mean	333.6	324.6	343.3	348.3	329.1
(SD)	(66.89)	(79.98)	(33.01)	(21.80)	(73.85)
Min, Max	1, 365	1, 364	183, 362	169, 364	1, 365
Exposure, n (%)					
≥ 1 day	268 (100.0)	273 (100.0)			541 (100.0)
≥ 15 days	266 (99.3)	268 (98.2)			534 (98.7)
≥ 29 days	264 (98.5)	265 (97.1)			529 (97.8)
≥ 57 days	262 (97.8)	263 (96.3)			525 (97.0)
≥ 85 days	260 (97.0)	260 (95.2)			520 (96.1)
≥ 113 days	256 (95.5)	258 (94.5)			514 (95.0)
≥ 169 days	254 (94.8)	252 (92.3)	125 (100.0)	127 (100.0)	506 (93.5)
≥ 225 days	250 (93.3)	245 (89.7)	120 (96.0)	125 (98.4)	495 (91.5)
≥ 281 days	248 (92.5)	242 (88.6)	118 (94.4)	124 (97.6)	490 (90.6)
≥ 351 days	216 (80.6)	216 (79.1)	107 (85.6)	109 (85.8)	432 (79.9)

N = number of subjects in the Safety Set 1; n = number of subjects
SD = standard deviation
[a] Based on the subjects in the Safety Set 2; Humira®/SB5 and Humira®/Humira® may not add up to Humira® overall.
Percentages were based on N.
Duration of exposure (days) was calculated as follows:
If the last IP administration date was known: (last IP administration date – first IP administration date) + 1
If the last IP administration date was unknown: (last visit date – first IP administration date) + 1

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Study SB5-G31-RA

Over the course of the study, there were small changes in the mean and median values for liver function tests (serum transaminases, albumin, total bilirubin, gamma glutamyl transferase (GGT) and lactate dehydrogenase) in both treatment groups that were clinically insignificant.

Up to Week 52, the most commonly reported abnormality of liver function tests was an elevated alanine transaminase (ALT) value (that is ≥ 2 fold upper limit of normal (ULN) increase), which was recorded in 3.7% (10/268) of subjects in the SB5 group, 5.5% (7/127) of patients in the continuous Humira arm and 6.4% (8/125) of subjects in the Humira to SB5 switch group. Increased aspartate transaminase (AST) readings ≥ 2 fold

ULN increase were observed in 1.5% (4/268) of subjects in the SB5 group, 0.8% (1/127) of patients in the continuous Humira arm and 3.2% (4/125) of subjects in the Humira to SB5 switch group. Four subjects (2 in each of the main treatment groups) reported increases in serum total bilirubin > 34 µmol/L. In addition, high GGT readings were reported in 4 subjects in each main treatment group (1.5%). There were no possible Hy's law cases observed in Study SB5-G31-RA.

Supporting studies

There were no clinically significant post dose changes in liver function tests in the two Phase I SB5 clinical studies. In Study SB5-G21-RA, 1 subject developed a post-treatment increase in serum total bilirubin (> 34.2 µmol/L) and another subject recorded a high serum ALT reading (> 99 U/L for female and > 123 U/L for men).

Renal function and renal toxicity

Study SB5-G31-RA

Over the 52 week treatment follow-up period of Study SB5-G31-RA, 3.2% (8/247) of subjects in the SB5 group and 6.2% (15/242) of patients in the overall Humira arm recorded minor shifts (increases) from a normal baseline value in serum creatinine levels on at least 1 occasion.

Supporting studies

No subjects in the single dose Phase I trials or the Phase II Study SB5-G21-RA developed clinically significant abnormalities in renal function.

Other clinical chemistry

Study SB5-G31-RA

Up to Week 52, high serum glucose readings > 13.9 mmol/L were reported in 2 subjects (0.7% of 268) in the SB5 group and 2 patients (0.7% of 273) in the overall Humira arm.

Supporting studies

No subjects in the single dose Phase I trials were identified as developing clinically significant abnormalities in biochemistry. One subject (2.0% of 49) in Study SB5-G21-RA recorded a high blood glucose result (> 250 mg/dL).

Haematology and haematological toxicity

Study SB5-G31-RA

In Study SB5-G31-RA, there were no notable differences between the 2 treatment groups for mean and median changes in haematology parameters. Up to Week 52 in the SAF population, a total of 9 patients developed low neutrophil cell counts of < 1.2 x 10^9/L (5 subjects (1.9% of 268) in the SB5 group, 1 (0.8% of 127) in the continuous Humira arm and 3 (2.4% of 125) in the Humira to SB5 switch group), 5 subjects developed decreases in lymphocyte cell counts of < 0.5 x 10^9/L (3 (1.1% of 268) in the SB5 group and 2 (1.6% of 127) in the continuous Humira arm) and 1 subject in in the SB5 arm recorded a low serum haemoglobin level (< 80 g/L for females and < 90 g/L for males). One subject in the SB5 treatment group (0.4% incidence) developed significant thrombocytopaenia (platelet count < 50 x 10^9/L) during Study SB5-G31-RA.

Supporting studies

No subjects in the single dose Phase I trials or the Phase II Study SB5-G21-RA were recorded as developing significant abnormalities in haematology parameters.

QuantiFERON Gold tests and latent Tuberculosis

Study SB5-G31-RA

No subjects in the SAF1 cohort had a positive QuantiFERON Gold test at screening in Study SB5-G31-RA. At Week 24, the majority of subjects in the SB5 (82.1%; 220/268) and the Humira (82.8%; 226/273) treatment groups had a negative result for QuantiFERON Gold testing. In the SB5 treatment group, 10 (3.7%) subjects had positive and 2 (0.7%) subjects had indeterminate results, and in the Humira arm 9 (3.3%) subjects had positive and 2 (0.7%) subjects had indeterminate results. In the SB5 treatment group, a total of 12 subjects (4.5%) were considered to have latent TB at Week 24, 10 of whom had a positive QuantiFERON Gold test result for the first time at Week 24, 1 subject had an indeterminate QuantiFERON Gold test result on 2 occasions and 1 subject whose QuantiFERON Gold test was not available for the first time because the sample was not centrifuged, recorded a positive test result on second testing. In the Humira arm, a total of 10 subjects (3.7%) were considered to have latent TB up to Week 24 including 9 subjects with a positive QuantiFERON Gold test result for the first time and 1 subject whose test was not available for the first time because the sample was not centrifuged, but positive for the second time. The 2 subjects with indeterminate QuantiFERON tests initially were not considered to have latent TB because their second test result was negative.

At Week 52, the QuantiFERON Gold test results were comparable between the treatment groups. The majority of subjects had a negative result: 225 (84.0%) subjects in the SB5, 226 (82.8%) subjects in the overall Humira cohort, 108 (86.4%) subjects in the Humira switching to SB5 group and 108 (85.0%) subjects in the continuous Humira treatment arm. Eleven (4.1%) subjects had positive and 1 (0.4%) subject had indeterminate results in the SB5 treatment group; 10 subjects (3.7%) had positive and 1 (0.4%) subject had indeterminate result in the overall Humira cohort. At Week 52, a total of 11 subjects (4.1%) in the SB5 treatment group were considered to have latent TB plus 4 subjects (3.2%) in the Humira switching to SB5 group and 6 (4.7%) in the continuous Humira group were considered to have latent TB.

Supporting studies

No subject in the supporting studies developed latent TB.

Electrocardiograph findings and cardiovascular safety

Study SB5-G31-RA

There were 2 cardiovascular related deaths (cardiac arrest and pulmonary embolism) in Study SB5-G31-RA, both of which occurred in Humira treated subjects before Week 24. In addition, 1 SB5 treated subject suffered an acute, non-fatal myocardial infarction up to Week 52 in this trial.

Supporting studies

In each of the supporting studies, no significant changes (mean, median or individual) in ECG parameters such as QT interval were observed. Minor alterations similar to that observed in healthy individuals over time were seen, but no subject developed clinically significant ECG changes over time after receiving adalimumab.

Vital signs and clinical examination findings

Study SB5-G31-RA

At Week 52, there were small differences between the SB5 and Humira treatment groups in mean systolic blood pressure (+1.1 mmHg and +2.1 mmHg, respectively), mean diastolic blood pressure (+1.3 mmHg and 0.5 mmHg, respectively) and heart rate (–0.5 bpm and -0.1 bpm, respectively). The clinical study report did not include information on the

changes in subject weight with treatment (mean and clinically significant changes in individual subjects).

At 24 weeks, 2 subjects in each treatment group recorded clinically significant, low systolic blood pressure (≤ 90 mmHg and a change from baseline ≤ –20 mmHg), 1 subject in the Humira arm reported clinically significant high systolic blood pressure (≥ 180 mmHg and a change from baseline ≥ 20 mmHg) and 3 subjects in the Humira group recorded clinically significant high diastolic readings (≥ 105 mmHg and a change from baseline ≥ 20 mmHg). The proportion of subjects who developed clinically significant changes in blood pressure between Weeks 24 and 52 was similar to that observed at Week 24.

Supporting studies

In all of the supporting studies, mean and median values for all vital sign parameters (such as systolic and diastolic blood pressure, heart rate and body temperature) did not show any significant change over time. In addition, no subject was observed to develop clinically significant changes in vital sign parameters in the 3 supporting trials.

Immunogenicity and immunological events

Methods

A single bridging ligand binding assay was used for the determination of Anti-Drug Antibodies (ADA) to adalimumab in the clinical Phase I and Phase III studies. In this assay, the qualitative and quasi-quantitative determination of ADA in human serum samples was conducted by using a validated Meso Scale Discovery (MSD) platform. In addition, a ligand binding assay was used for the determination of NAbs in the clinical studies. Neutralising activity was assessed by inhibition, represented by the normalised ratio of binding of adalimumab to TNF present in the blood samples. In the SB5 study program, only serum samples with a positive ADA result were further analysed for NAbs. Moreover, method validation of the ADA and NAb assays indicates that Hadlima and EU or US Humira were antigenically equivalent.

The evaluator notes that the incidence of ADA depends on a number of factors, including disease state, type of assay, assay sensitivity and interference by free drug. Assays for ADA must also avoid interference by RF and heterophile antibody. The immunogenicity evaluation of Hadlima was conducted using an appropriately developed and validated method of investigation, which was fittingly outlined in the submission.

Study SB5-G31-RA

In Study SB5-G31-RA, blood samples for immunogenicity testing were collected at baseline and Weeks 4, 8, 16, 24, 32, 40 and 52. An ADA result was defined as positive if the patient had at least 1 ADA positive result until the relevant time point among the subjects with an ADA negative result at Week 0, and was deemed negative if a patient had no ADA positive result until the relevant time point of interest. The incidence of ADA and NAb up to Week 24 in Study SB5-G31-RA is presented in Table 4. At 24 Weeks, there was no statistically significant difference between the 2 treatment groups in ADA results (p-value = 0.816) with 32.1% (79/246) patients in the SB5 group and 31.2% (81/260) patients in the Humira arm with an overall ADA positive result. At 24 weeks, 32 patients in the SB5 group and 32 patients in the Humira arm tested positive for NAbs. In Study SB5-G31-RA, 5.0% (27/538) of all enrolled patients had positive ADA results at baseline. Of the 19 patients in the SB5 group with positive ADA at Week 0 (plus another subject had a missing result), 9 patients (45.0%) had treatment boosted ADA (that is the ADA titre increased at any time post-baseline compared with the baseline titre), 9 patients (45.0%) had positive ADA where the titre remained either the same or decreased compared with their baseline titre and the other 2 patients (10.0%) had negative ADA results at all visits after study drug administration. Of the 9 patients in the Humira arm with positive ADA or missing result at Week 0, 5 patients (55.6%) had treatment boosted ADA (including

1 subject with a missing value at baseline and positive result post-baseline), 1 patient (11.1%) had persistent positive ADA of the same or lower titre and 3 subjects (33.3%) had negative ADA at all visits after receiving Humira.

Table 4: Incidence of ADA and NAb up to Week 24 in Study SB5-G31-RA

Timepoint	Parameter	Result	SB5	EU Humira®			Total
				Overall	SB5	EU Humira®	
			N=268	N=273	N=125[a]	N=127[a]	N=541
			n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)
Week 0	ADA	Positive	19/267 (7.1)	8/271 (3.0)	3/125 (2.4)	3/126 (2.4)	27/538 (5.0)
		Negative	248/267 (92.9)	263/271 (97.0)	122/125 (97.6)	123/126 (97.6)	511/538 (95.0)
	NAb	Positive	1/19 (5.3)	0/8 (0.0)	0/3 (0.0)	0/3 (0.0)	1/27 (3.7)
		Negative	18/19 (94.7)	8/8 (100.0)	3/3 (100.0)	3/3 (100.0)	26/27 (96.3)
Week 4	ADA	Positive	61/265 (23.0)	38/269 (14.1)			99/534 (18.5)
		Negative	204/265 (77.0)	231/269 (85.9)			435/534 (81.5)
	NAb	Positive	12/61 (19.7)	6/38 (15.8)			18/99 (18.2)
		Negative	49/61 (80.3)	32/38 (84.2)			81/99 (81.8)
Week 8	ADA	Positive	44/263 (16.7)	31/266 (11.7)			75/529 (14.2)
		Negative	219/263 (83.3)	235/266 (88.3)			454/529 (85.8)
	NAb	Positive	19/44 (43.2)	14/31 (45.2)			33/75 (44.0)
		Negative	25/44 (56.8)	17/31 (54.8)			42/75 (56.0)
Week 16	ADA	Positive	60/258 (23.3)	60/261 (23.0)			120/519 (23.1)
		Negative	198/258 (76.7)	201/261 (77.0)			399/519 (76.9)
	NAb	Positive	25/60 (41.7)	26/60 (43.3)			51/120 (42.5)
		Negative	35/60 (58.3)	34/60 (56.7)			69/120 (57.5)
Week 24	ADA	Positive	67/256	67/257	35/125	31/127	134/513
			(26.2)	(26.1)	(28.0)	(24.4)	(26.1)
		Negative	189/256 (73.8)	190/257 (73.9)	90/125 (72.0)	96/127 (75.6)	379/513 (73.9)
	NAb	Positive	32/67 (47.8)	32/67 (47.8)	15/35 (42.9)	17/31 (54.8)	64/134 (47.8)
		Negative	35/67 (52.2)	35/67 (52.2)	20/35 (57.1)	14/31 (45.2)	70/134 (52.2)
Week 24 Overall[b]	ADA	Positive	79/246 (32.1)	81/260 (31.2)	42/122 (34.4)	35/123 (28.5)	160/506 (31.6)
		Negative	167/246 (67.9)	179/260 (68.8)	80/122 (65.6)	88/123 (71.5)	346/506 (68.4)

The percentages of subjects who experienced any AE and the types of AEs most commonly reported were comparable between the Hadlima and Humira treatment groups in subjects with negative and positive ADA results at Week 24.

The incidence of ADA and NAb up to Week 52 in Study SB5-G31-RA is presented in Table 5. Up to 52 weeks in the SAF2 cohort, there was no statistically significant difference between the 2 continuous treatment groups in the proportion of subjects testing at least

once positive for ADA (p-value = 0.796) with 36.0% (85/236) patients in the continuous Hadlima group and 37.4% (46/123) patients in the Humira arm recording a positive ADA result. At 52 weeks, the Humira to Hadlima treatment switch group of patients had a similar rate of ADA positivity (38.5%; 47/122) to the 2 continuous treatment groups. Between Weeks 24 and 52, there was no statistically significant difference (p-value = 0.161) between Humira to Hadlima switch group (6.3%; 5/80) and continuous Humira treatment groups (12.6%; 11/87) for the proportion of subjects developing a new positive ADA result (SAF2 cohort).

Among the 45 patients in the Humira to Hadlima group with positive ADA at Week 24, 16 patients (35.6%) recorded treatment boosted positive ADA results between Weeks 24 and 52 upon transitioning of treatment, 22 patients (48.9%) had persistent positive ADA where the titre remained either the same or decreased compared with their baseline titre and the other 7 patients (15.6%) had negative ADA results at all subsequent visits. Of the 39 patients in the continuous Humira arm with positive ADA or missing results at Week 24, 12 patients (30.8%) had treatment boosted ADA, 23 patients (59.0%) had persistent positive ADA of the same or lower titre and 4 subjects (10.3%) had negative ADA at all visits after Week 24 despite continuing to receive Humira.

At 52 weeks, 32 patients (50% of 64) in the Hadlima group and 41 patients (54.7% of 75) in the overall Humira cohort tested positive for NAbs.

The percentages of subjects who experienced any AE and the types of AEs most commonly reported (including ISRs) were comparable between the continuous Hadlima and Humira treatment groups, as well as the Humira to Hadlima treatment switch arm after Week 24, in subjects with negative and positive ADA results anytime up to Week 52.

At baseline in Study SB5-G31-RA, the majority of subjects in the SB5 (95.1%; 254/267) and the Humira (94.9%; 258/272) treatment groups had negative ANA (anti-nuclear antibody) tests. At Week 24, 12 (4.6%) subjects in the SB5 group and 13 (5.0%) subjects in the Humira arm recorded new post-baseline positive ANA results. At Week 52, shifts from negative ANA at baseline to positive results was reported in 21 (8.4%) SB5 treated subjects and 25 (10.0%) patients in the overall Humira cohort (14 subjects (11.4%) in the Humira® SB5 group and 11 patients (8.8%) in the continuous Humira subgroup). At Week 24, a total of 3 and 5 subjects in the SB5 and Humira treatment groups, respectively, tested positive for anti-dsDNA antibodies. At Week 52, 6 subjects in the SB5 arm and 2 in the overall Humira cohort (including 1 subject in each of the subgroups) tested positive for anti-dsDNA antibodies. Despite the rates of positive ANA and anti-dsDNA serology (within expectations for anti-TNF therapy treated subjects with RA), no subject in Study SB5-G31-RA developed a lupus like clinical illness.

Table 5: Incidence of ADA and NAb up to Week 52 in Study SB5-G31-RA

			SB5 40 mg	Humira® 40 mg			Total
				Overall	SB5 40 mg	Humira® 40 mg	
			N=268	N=273	N=125[a]	N=127[a]	N=541
Timepoint	Parameter	Result	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)
Week 32	ADA	Positive	69/254 (27.2)	80/253 (31.6)	41/125 (32.8)	38/126 (30.2)	149/507 (29.4)
		Negative	185/254 (72.8)	173/253 (68.4)	84/125 (67.2)	88/126 (69.8)	358/507 (70.6)
	NAb	Positive	29/69 (42.0)	34/80 (42.5)	15/41 (36.6)	19/38 (50.0)	63/149 (42.3)
		Negative	40/69 (58.0)	46/80 (57.5)	26/41 (63.4)	19/38 (50.0)	86/149 (57.7)
Week 40	ADA	Positive	67/249 (26.9)	78/244 (32.0)	38/119 (31.9)	40/125 (32.0)	145/493 (29.4)
		Negative	182/249 (73.1)	166/244 (68.0)	81/119 (68.1)	85/125 (68.0)	348/493 (70.6)
	NAb	Positive	27/67 (40.3)	41/78 (52.6)	21/38 (55.3)	20/40 (50.0)	68/145 (46.9)
		Negative	40/67 (59.7)	37/78 (47.4)	17/38 (44.7)	20/40 (50.0)	77/145 (53.1)
Week 52	ADA	Positive	62/247 (25.9)	75/242 (31.0)	35/118 (29.7)	40/124 (32.3)	139/489 (28.4)
		Negative	183/247 (74.1)	167/242 (69.0)	83/118 (70.3)	84/124 (67.7)	350/489 (71.6)
	NAb	Positive	32/64 (50.0)	41/75 (54.7)	18/35 (51.4)	23/40 (57.5)	73/139 (52.5)
		Negative	32/64 (50.0)	34/75 (45.3)	17/35 (48.6)	17/40 (42.5)	66/139 (47.5)
Week 52 overall[b]	ADA	Positive	88/246 (35.8)	97/260 (37.3)	47/122 (38.5)	46/123 (37.4)	185/506 (36.6)
		Negative	158/246 (64.2)	163/260 (62.7)	75/122 (61.5)	77/123 (62.6)	321/506 (63.4)
After Week 24 overall[c,d]	ADA	Positive	9/160 (5.6)	16/167 (9.6)	5/80 (6.3)	11/87 (12.6)	25/327 (7.6)
		Negative	151/160 (94.4)	151/167 (90.4)	75/80 (93.8)	76/87 (87.4)	302/327 (92.4)
Week 52 overall[b,c]	ADA	Positive	85/236 (36.0)	93/245 (38.0)	47/122 (38.5)	46/123 (37.4)	178/481 (37.0)
		Negative	151/236 (64.0)	152/245 (62.0)	75/122 (61.5)	77/123 (62.6)	303/481 (63.0)

N = number of subjects in the Safety Set 1; n = number of subjects with event of interest, n' = number of subjects with available ADA results against SB5 at each timepoint

ADA = anti-drug antibody, NAb = neutralising antibody

[a] Based on the subjects who had re-randomisation at Week 24 among the Safety Set 1; Humira®/SB5 and Humira®/Humira® may not add up to Humira® overall.

[b] Overall ADA results were determined as 'Positive' if subject had at least 1 ADA positive until the relevant timepoint among the subjects with ADA Negative result at Week 0 and 'Negative' if subject had no ADA positive until the relevant timepoint.

[c] Values were from the Safety Set 2.

[d] After transition overall were determined as 'Positive' if subject had at least one ADA positive from Week 32 to Week 52 among subjects with the overall ADA negative at Week 24 and 'Negative' if subject had no ADA positive from Week 32 to Week 52 among subjects with the overall ADA negative at Week 24.

Percentages were based on n'.

Study SB5-G11-NHV

A total of 189 healthy subjects aged 18 to 55 years were enrolled and randomised into this Phase I study (63 subjects in each group). Blood samples were collected pre-dose, and Days 15 and 71 to determine ADA and NAb to adalimumab following a single dose of SB5, EU Humira or US Humira. At baseline pre-dose, 12 subjects were positive for ADA: 5 subjects in the SB5 group, 2 in the EU Humira arm and 5 subjects in the US Humira group.

As summarised in Table 6, the majority of subjects (> 95% in each of the 3 treatment groups) developed ADA post dose with no statistical differences between the arms for the incidence of ADA. The incidence of post dose NAbs was also high in each of the treatment groups with no statistically significant differences between the arms. In the SB5 group, 79.0% (49/62) of subjects had a positive result for NAb, which was numerically slightly lower than that reported for the 2 Humira groups (80.0% (48/60) for EU Humira and 82.5% (52/63) for US sourced Humira).

Overall, 176 AEs were reported in 103 (54.5% of 189) ADA positive subjects compared to 3 AEs recorded in 1 (0.5% of 189) ADA negative subjects. Like the overall study cohort, the 2 most common types of AEs by Preferred Term (PT) reported in ADA positive subjects were nasopharyngitis (30 AEs in 30 subjects) and headache (26 AEs in 22 subjects).

Table 6: Incidence of ADA and NAb at each tested time point in Study SB5-G11-NHV

Parameter	Time Point	Result	SB5 N=63	EU Humira® N=63	US Humira® N=63	Total N=189
			n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)
Anti-drug Antibodies (ADA)	Day 1 pre-dose	Positive	5/63 (7.9)	2/63 (3.2)	5/63 (7.9)	12/189 (6.3)
		Negative	58/63 (92.1)	61/63 (96.8)	58/63 (92.1)	177/189 (93.7)
	Day 15	Positive	43/63 (68.3)	46/63 (73.0)	41/63 (65.1)	130/189 (68.8)
		Negative	20/63 (31.7)	17/63 (27.0)	22/63 (34.9)	59/189 (31.2)
	Day 71	Positive	61/63 (96.8)	59/63 (93.7)	62/63 (98.4)	182/189 (96.3)
		Negative	2/63 (3.2)	4/63 (6.3)	1/63 (1.6)	7/189 (3.7)
	Post-dose (Total)	Positive	62/63 (98.4)	60/63 (95.2)	63/63 (100.0)	185/189 (97.9)
Neutralising Antibodies (NAb)	Day 1 pre-dose	Positive	0/5 (0.0)	0/2 (0.0)	1/5 (20.0)	1/12 (8.3)
		Negative	5/5 (100.0)	2/2 (100.0)	4/5 (80.0)	11/12 (91.7)
	Day 15	Positive	1/43 (2.3)	1/46 (2.2)	1/41 (2.4)	3/130 (2.3)
		Negative	42/43 (97.7)	45/46 (97.8)	40/41 (97.6)	127/130 (97.7)
	Day 71	Positive	49/61 (80.3)	48/59 (81.4)	51/62 (82.3)	148/182 (81.3)
		Negative	12/61 (19.7)	11/59 (18.6)	11/62 (17.7)	34/182 (18.7)
	Post-dose (Total)	Positive	49/62 (79.0)	48/60 (80.0)	52/63 (82.5)	149/185 (80.5)

ADA = Anti-drug antibodies; NAb = Neutralising antibodies; N = number of subjects in the Safety set;
n = number of subjects with applicable result; n' = number of subjects with available assessment results at each timepoint.
Percentages for ADA result were based on the number of subjects with available ADA assessment results at each time point.
Percentages for NAb result at each time point were based on the number of subjects with positive ADA at each relevant time point.

Other safety issues

Safety in special populations

No pregnancies were reported during the clinical Phase I and III studies with Hadlima, and the proposed PI is consistent with the reference drug (Humira) in recommending that women of childbearing potential use adequate contraception during and for at least 5 months after their last adalimumab injection.

There is no available information on the safety of adalimumab in the setting of administration of live vaccines and the sponsor has acknowledged this in the submission and the proposed PI. There is also limited safety experience in patients undergoing surgical procedures (including elective joint arthroplasty). Study SB5-G31-RA excluded subjects with a history of an infected joint prosthesis, which has not been removed or replaced. Patients with known hypersensitivity to adalimumab or other components of Humira were not included in the clinical studies for Hadlima as the prior use of any biologic DMARD (including Humira) was an exclusion criterion.

Subgroup analysis of overall treatment emergent AEs in the safety population in Study SB5-G31-RA (up to 52 weeks of drug exposure) has not revealed any potential risk factors for overall AEs. However, there is a slightly higher incidence of AEs in the System Organ Class (SOC) of infection for older patients (age > 65 years versus < 65 years), which is an expected finding regardless of therapy for RA.

Safety related to drug-drug interactions and other interactions

Consistent with the EMA guideline on biosimilar medicines, the sponsor has not conducted any specific drug-drug interaction studies with Hadlima. In the proposed PI and CMI, the sponsor has included the warning recommendation of the Humira PI stating that concurrent administration of adalimumab with other biologic DMARDs (in particular, anti-TNF drugs and anakinra) is not recommended as studies have shown an increased risk of serious infection with no added clinical benefit.

Post-marketing data

Not applicable as Hadlima has not been approved or marketed in any country as of yet. However, there is a large volume of long-term clinical experience with Humira in the requested treatment indications to indicate that if Hadlima meets the criteria for biosimilarity with Humira (reference product), then a predictable positive benefit: risk assessment can be concluded.

Evaluator's conclusions on safety

The safety profile of anti-TNF drugs, including adalimumab, is well characterised in the published literature. In this submission for the registration of Hadlima (SB5) (biosimilar medicine of Humira), the principal safety population consisted of 541 adult patients with active RA who received at least 1 dose of either SB5 or EU sourced Humira during the Phase III clinical trial SB5-G31-RA. Of these patients, 268 received treatment with SB5 for a mean duration of 334 days (11 months) and 273 subjects were given Humira for a mean duration of 325 days (10.5 months). In addition, 379 healthy subjects aged between 18 and 55 years were evaluated in the 2, single dose, Phase I studies (SB5-G11-NHV and SB5-G12-NHV) and 49 subjects with RA received up to 6 doses of 40 mg of SB5 fortnightly. Overall, the size of the safety population and the duration of exposure to SB5 meet the regulatory guidelines (CPMP/EWP/556/95rev1/FINAL) for presenting a safety population of sufficient size and follow-up duration to assess for possible registration.

The most frequently reported treatment emergent AEs (experienced by ≥ 5% of patients) in Study SB5-G31-RA were in the SOCs of infection, musculoskeletal disorders, nervous system disorders, abnormal investigations (for example raised liver enzymes and various haematological abnormalities) and general disorders and administration site conditions (mainly, injection site reactions). The frequency and severity of treatment emergent AEs in Study SB5-G31-RA was comparable between the SB5 and Humira treatment groups apart from a higher incidence of nasopharyngitis with EU sourced Humira (9.2%) versus SB5 (4.9%) up to Week 24. In the 3 supporting studies, in particular Study SB5-G11-NHV, a similar pattern of the most commonly reported treatment emergent AEs was observed in all treatment groups (SB5 therapy, EU sourced and US sourced Humira). The most

common treatment emergent AEs by PT in healthy volunteers were nasopharyngitis, headache, oral herpes infection and rhinitis. In Study SB5-G31-RA, injection site reactions and erythema were the 2 most frequent types of treatment related AEs at the PT level up to Week 24 and occurred at an approximate 3 fold increased incidence in the Humira group (1.5% incidence for both AEs) compared with SB5 (≤ 0.4% incidence).

Given the mechanism of action of adalimumab, infection is an AE of special interest. The overall number of subjects experiencing infection related AEs (17.2 to 18.3%) was comparable between the 2 treatment groups in Study SB5-G31-RA. In addition, the number of infection related serious adverse events (SAEs) was similar between the 2 treatment groups. Up to Week 52 in Study SB5-G31-RA, 4 subjects in each treatment group developed latent TB (even after careful screening at baseline for latent TB reactivation). In supporting studies, infection related AEs affected > 20% of all subjects with no clear discernible differences in the pattern and type of infection observed in healthy volunteers treated with the various formulations of adalimumab and the mode of administration.

Two patients treated with Humira died in Study SB5-G31-RA (cardiac arrest and pulmonary embolism), but neither fatality was considered by the site investigators to be related to Humira. Malignant neoplasms were reported in 4 (0.8%) patients after Week 24; (2 subjects in the Humira/ Humira treatment group, 1 subject in the Humira/ SB5 treatment group (considered to be undetermined, as a lag time window overlapped with pre transition IP (Humira) exposure time period) and 1 subject in the SB5/SB5 treatment group)in Study SB5-G31-RA. The observed rate and pattern of drug-related, treatment-emergent SAEs was similar for both treatment groups in Study SB5-G31-RA.

In the pivotal Phase III clinical trial, the frequency of patients who were discontinued due to drug-related AEs was low and similar between the 2 treatment groups (up to 5.5% at 52 weeks in Study SB5-G31-RA). The most frequent type of AE leading to permanent study treatment discontinuation in Study SB5-G31-RA was skin rash. However, other reasons for discontinuation from adalimumab in Study SB5-G31-RA included infection, hypersensitivity reactions, ISRs and positive QuantiFERON Gold tests for TB.

Injection site reactions were reported in all clinical studies (all treatment groups). Up to Week 52 in Study SB5-G31-RA, a total of 54 injection site AEs were recorded at a similar frequency among the treatment groups (2.9 to 3.1% of subjects in each arm were affected). The most commonly reported types of ISRs at the PT level were injection site reactions and injection site erythema. In Study SB5-G11-NHV, only 1 treatment related ISR was reported in a subject who received US sourced Humira. Study SB5-G21-RA also showed a similar rate of ISR with SB5 administered by either AID or PFS.

In Study SB5-G31-RA, 3.7-6.4% of subjects developed ≥ 2 fold increases in serum transaminases at a slightly higher incidence with Humira therapy versus SB5. The majority of these AEs were not treatment related and probably do not reflect a true safety difference between the 2 formulations of adalimumab. In addition, there were a few significant cases of neutropenia and thrombocytopenia recorded in both adalimumab treatment groups of Study SB5-G31-RA. These cases are consistent with the Australian PI for Humira and published literature.

The incidence of subjects developing anti-ADA antibodies was comparable between Hadlima and Humira, and the clinical relevance of ADA is yet to be fully defined with no discernible link to the risk of infection, injection site related reactions or any other significant safety concern. By Week 52 in Study SB5-G31-RA, there was a statistically equivalent rate of positive ADA results in the overall Humira group (38.0%; 93/245) compared to Hadlima therapy (36.0%; 85/236). About half of all subjects who were ADA positive also tested positive for neutralising antibodies. The majority of patients (in both treatment groups) who tested positive for ADA did so at Week 16 of therapy, and ADA

positivity persisted throughout the trial. By Day 71 in Study SB5-G11-NHV, > 95% of subjects in each of the 3 treatment groups (SB5, EU sourced Humira and US sourced Humira) tested positive for ADA, and the majority of ADA positive subjects also tested positive for NAb.

In Study SB5-G31-RA, a total of 3 malignant neoplasms were reported: 2 in Humira treated patients (lymphoma with spinal metastases, and papillary thyroid cancer) and 1 in a treatment switch subject (glioblastoma multiforme). Another Humira treated subject developed seminoma on study Day 313 which required orchiectomy. Only 1 lymphoproliferative disorder was reported in this submission although this is a potential identified risk for anti-TNF therapy that is outlined in the RMP and the proposed Australian PI. Other previously identified safety concerns with adalimumab such as lupus-like syndromes and demyelinating disorders were not reported in any of the studies in the SB5 trial program.

The analysis of AEs reported during treatment with Hadlima and the reference product Humira in Studies SB5-G31-RA, SB5-G12-RA, SB5-G11-NHV and SB5-G12-NHV has not revealed any significant differences in the incidence and type of AEs. Moreover, no new safety signals have emerged from the submitted dataset to indicate the known risk profile of adalimumab has altered. The current safety dataset for Hadlima is limited to 60 weeks of treatment follow-up and it would be important to continue collecting data beyond this time frame as part of post-marketing pharmacovigilance if approval was granted. Nonetheless, the safety data for Humira exceeds 18 years of treatment follow-up and it is likely that Hadlima will demonstrate a similar safety profile over longer term follow-up based on the similar short term safety experience between the 2 formulations of adalimumab. However, as Study SB5-G31-RA recruited subjects with active RA who were meticulously screened for risks of immunosuppression, it is unclear if both formulations of adalimumab will demonstrate a similar safety profile in all of the patient populations for which Humira is currently approved.

First round benefit-risk assessment

First round assessment of benefits

Table 7 summarises the assessment of benefits at the first round.

Table 7: First round assessment of benefits

Indication: RA	
Benefits	**Strengths and Uncertainties**
Hadlima produces improvements in the symptoms and signs of active RA (as per the ACR clinical response criteria) that is comparable to Humira.	Observed data in the Phase III trial; Study SB5-G31-RA. About 70% of RA patients achieve ACR20 response (that is the minimal clinically detectable improvement) at Week 24, which is consistent with other approved biologic DMARD therapies.
Hadlima results in improved physical function in patients with active RA (as per HAQ-DI responses) that is comparable to Humira.	Observed data in the Phase III trial; Study SB5-G31-RA. The magnitude of benefit is clinically meaningful and consistent with other biologic DMARD therapies.

Indication: RA	
Benefits	**Strengths and Uncertainties**
Hadlima and Humira result in statistically equivalent lower rates of structural RA disease progression at 52 weeks versus expected rates of X-ray progression in historical cohorts.	Observed data in the Phase III trial; Study SB5-G31-RA. Although the small increases from baseline in mTSS reflect statistical inhibition of X-ray progression, the clinical significance of this finding is unclear.
Persistence of clinical response for up to 52 weeks in the subgroup of RA patients who are tolerating and responding to Hadlima 40 mg SC fortnightly (for example ACR20 response rate of 76.9% and ACR50 response > 50% at 52 weeks).	Observed data in the Phase III trial; Study SB5-G31-RA. No ongoing long term trial data has been provided or offered in the future. Follow-up to 52 weeks of treatment provides medium term experience but multi-year (≥ 2 years) follow-up is better.
Convenient schedule and administration mode (SC injection fortnightly) with choice of 2 administration devices; PFS and AID.	Supported by PK data for both devices. Alternative biologic DMARD therapy may require IV drug administration.
High rates of patient satisfaction and preference plus usability responses with Hadlima therapy given by AID versus PFS.	Supported by the Phase II clinical study SB5-G21-RA.

First round assessment of risks

Table 8 summarises the first round assessment of risks at the first round.

Table 8: First round assessment of risks

Risks	Strengths and Uncertainties
Increased incidence of serious and opportunistic infection, including latent TB with Hadlima which is comparable to that observed with Humira.	Observed data in the Phase III Study SB5-G31-RA. Despite meticulous screening, several cases of latent TB were seen in both adalimumab treatment groups.
Increased incidence of injection site reactions with Hadlima that is comparable to (and possibly less frequent) than Humira	Observed data in the Phase III Study SB5-G31-RA plus 2 supporting studies (SB5-G21-RA and SB5-G11-NHV).
Increased incidence of permanent treatment discontinuations due to AEs with Hadlima that is comparable (and possibly lower) versus Humira.	This was observed in the Phase III clinical study.
Increased incidence of haematological abnormalities such as neutropenia and thrombocytopenia with Hadlima versus PBO, that is comparable to adalimumab.	Observed in Phase III clinical trial. This is known safety information which is included in the proposed PI and RMP for Hadlima.

Risks	Strengths and Uncertainties
Comparable (but relatively high) rates of anti-drug antibody formation with Hadlima and Humira suggesting equivalence in immunogenicity.	This was consistently observed in the Phase I and III clinical studies in which ADA was assessed. Study SB5-G31-RA had much lower rates of ADA than Study SB5-G11-NHV suggesting concomitant MTX may reduce the incidence of ADA formation.
Potential for diminished clinical efficacy if patient develops medium to high titres of ADA as this has been shown to reduce trough drug levels. Sponsor included information in to indicate trough drug level is an important determinant of clinical response.	The sponsor has conducted a post hoc analysis of ADA formation on the PK of Hadlima and Humira using data from the Phase I and III clinical studies. The PI does not contain specific information on this issue.
Hadlima has not been studied in patients < 18 years of age, in subjects with significant organ dysfunction, those with concurrent Hepatitis B or C virus or HIV, and in pregnant/lactating women.	The populations with inadequate clinical data regarding Hadlima therapy are appropriately identified in the proposed RMP.

First round assessment of benefit-risk balance

The submission indicates that the benefit-risk balance of Hadlima is favourable for the treatment of active RA in adult patients, who have had an inadequate response to treatment with MTX (Study SB5-G31-RA). The currently available dataset on the benefit-risk balance of Hadlima in adult patients with RA is limited to 60 weeks of treatment follow-up (including 52 weeks of active drug treatment). This submission also contains a sufficient volume of data to support the claim that Hadlima is pharmacokinetically equivalent to the reference product, Humira, in adult patients with active RA (Study SB5-G31-RA) and in healthy young-middle aged subjects (Studies SB5-G11-NHV and SB5-G12-NHV).

The sponsor has provided a review of the literature on the role of TNF in the disorders covered by the therapeutic indications of Humira, and the potential mechanisms by which adalimumab exerts its clinical efficacy. The mechanism of action of adalimumab is complex but the primary mode of action results from direct blocking of TNF receptor-mediated biological activities. Adalimumab is a recombinant monoclonal antibody that competitively inhibits TNF by binding to it, thereby blocking the interaction between TNF and TNF receptors. This is thought to prevent various pro-inflammatory cellular responses that are recognised to occur in autoimmune conditions ranging from RA to AS and PSOR. [Information redacted].

On the safety aspect, there is an increased risk of infection (overall and serious) with Hadlima, which appears to be comparable to Humira. The submitted studies show a risk of injection site reactions with Hadlima, which is numerically lower than that observed with Humira therapy. There are limitations to the current dataset, which will require ongoing pharmacovigilance. The efficacy and safety of Hadlima in patients at a high risk of infection is not established. In addition, there is limited information about the safety and efficacy of switching to Hadlima from Humira, or vice versa. Multiple treatment switches between the 2 formulations of adalimumab is also an area of uncertainty, but there are at least theoretical concerns that such practice may increase the rates of immunogenicity.

Furthermore, the current dataset has evaluated Hadlima use in healthy volunteers and adult subjects with active RA and the submission included limited or no information (clinical and pharmacokinetic) on the use of Hadlima in other adult treatment indications or in children and adolescents with inflammatory conditions where Humira is also approved for use.

First round recommendation regarding authorisation

The clinical evaluator recommended acceptance of the sponsor's proposed registration of Hadlima to include RA as well as all of the current approved adult treatment indications for Humira. The current submission provides evidence that Hadlima is therapeutically equivalent to Humira in improving the signs and symptoms, as well radiographic outcomes in adult patients with active RA that are inadequately responding to MTX. This target treatment population is consistent with the approved RA treatment population for Humira. In addition, the applicant has provided data and a literature review assessment.

Satisfactory response to the questions raised is a recommended condition prior to further consideration of the proposed registration of Hadlima. At present, the supporting dataset for Hadlima is limited to patients with active RA and healthy adult volunteers. Moreover, there is no direct data with Hadlima use in a paediatric population and the overseas paediatric plans are > 5 years from reporting.

Second round benefit-risk assessment

In the response, the sponsor requests a change in the indications claimed in the current submission for Hadlima. Registration is now only being sought for RA in Australia and the sponsor recommends removal of all other proposed treatment indications. The applicant states that the removal of the request to seek extrapolation to other treatment indications for Hadlima is based on potential legal actions relating to patent protection rather than clinical concerns.

The revised proposed indications are:

> *Rheumatoid Arthritis*
>
> *Hadlima 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.*
>
> *Hadlima can be used alone or in combination with methotrexate.*

Second round assessment of benefits

After consideration of the responses to the clinical questions, the potential benefits of Hadlima in the proposed usage are consistent with those detailed in the first round assessment of benefits. In particular, the sponsor has provided further details about the preceding and concomitant RA treatments for the population recruited into the single pivotal clinical efficacy trial (Study SB5-G31-RA). Although the enrolled cohort of Study SB5-G31-RA is consistent with the RA population approved to receive treatment with Humira, it can be argued that the adequacy of preceding DMARD therapy (namely, sub-optimal MTX dosing and limited use of combination treatment strategies) was sub-optimal in many subjects regarding Australian clinical practice standards and international RA treatment guideline recommendations (for example EULAR endorsed). Hence, the external validity of the trial's results has limitations.

Additional analysis of the X-ray data obtained in Study SB5-G31-RA shows that Hadlima exhibits comparable efficacy to Humira in slowing the rate of structural disease progression over 52 weeks of therapy. The applicant has also provided quality assurance data on X-ray reader reliability to confirm that the observations were scientifically robust. The sponsor has outlined in the response to questions sufficient justification for extrapolation of the results of Study SB5-G31-RA (in subjects with active RA) to the other Humira approved adult treatment indications. However, the sponsor is now no longer seeking registration in the non-RA indications for allegedly legal reasons. It remains unclear to the clinical evaluator how the current lack of alternative Hadlima presentations to the 40 mg/0.8 mL vial may have impacted upon the registration of the three initially proposed paediatric treatment indications.

Second round assessment of risks

After consideration of the responses to the clinical questions (principally, Question 11), the risks of Hadlima are unchanged from those identified in the first round assessment of risks. Although it is disappointing that the sponsor is not proposing a specific post-marketing study or patient registry for Hadlima therapy in Australia, the proposed pharmacovigilance strategies meet the minimum standards for consideration of registration. The increased rate of serious and opportunistic infection with adalimumab versus PBO; as well as the higher incidence of permanent treatment discontinuation due to AEs and cytopenias remain a consistent safety signal, which is comparable between the 2 adalimumab formulations (Hadlima and Humira). Additionally, the lack of alternative Hadlima presentations to the 40 mg/0.8 mL vial significantly increases the risk of off label Hadlima use in Australia, particularly because the applicant has proposed withdrawing from seeking any other treatment indication approved for Humira other than the treatment of RA in adults.

Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, there is no change to the opinion expressed in the first round assessment of benefit-risk balance. On the basis of biosimilarity, the overall benefit-risk balance of Hadlima treatment (alone or in combination with MTX) in the sole proposed treatment indication of active RA is favourable. Clinically relevant efficacy has been directly observed with Hadlima therapy in the second line treatment RA population, but the external validity of the pivotal trial (Study SB5-G31-RA) results has some limitations to contemporary Australian practice and internationally accepted RA treatment guidelines (such as EULAR). The major risks with Hadlima therapy (versus PBO) are similar to the reference drug (Humira), and include an increased risk of serious infection, injection site reactions, neutropenia and thrombocytopenia.

Second round recommendation regarding authorisation

The clinical evaluator recommended acceptance of the sponsor's proposed registration of Hadlima to include the treatment of active RA in adult patients. The submission provides evidence that Hadlima is therapeutically equivalent to Humira in improving the signs and symptoms, as well radiographic outcomes in adult patients with active RA that are inadequately responding to MTX. This target treatment population is consistent with the main approved RA treatment population for Humira. In terms of safety, the 2 formulations of adalimumab appear to be clinically equivalent for the incidence and type of clinically significant safety concerns. The Hadlima clinical study program shows a low incidence of injection site reactions, and comparable immunogenicity in RA patients treated with

Hadlima compared to Humira. Moreover, the safety profile (incidence and type) of Hadlima is within historical expectations for Humira therapy in the target population.

In the second round evaluation, the sponsor is no longer seeking registration for Hadlima in any of the other 8 approved treatment indications for Humira. The applicant states this is due to legal (patent) concerns. However, there is significant concern for the implications that the applicant is not providing alternative Hadlima presentations to the 40 mg/0.8 mL vial, which has the potential for prescribing and dispensing errors, as well as increases the risk of off label use occurring with the registration of 2 adalimumab formulations in Australia. This is compounded by the sponsor only seeking registration in 1 of the 9 approved Humira treatment indications.

The clinical evaluator recommended that approval of the sponsor's proposed registration for Hadlima be subject to regular periodic safety update reports.

VI. Pharmacovigilance findings

Summary of RMP evaluation[18]

- The sponsor has submitted EU-RMP version 1.2 dated 11 May 2017; data lock point (DLP) 1 December 2015) and Australian Specific Annex (ASA) version 3.0 dated 17 October 2017.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies in Australia are summarised below in Table 9.

Table 9: Summary of risk management plan

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	infection, for example invasive fungal infections, parasitic infections, legionellosis and TB	ü	ü[1, 2]	ü	ü[3, 4]
	Reactivation of hepatitis B	ü	–	ü	ü[3, 4]
	Pancreatitis	ü	–	ü	–
	Lymphoma	ü	–	ü	ü[3, 4]
	HSTCL	ü	–	ü	ü[3, 4]
	Leukaemia	ü	–	ü	ü[3, 4]

[18] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	NMSC	ü	–	ü	ü[3, 4]
	Melanoma	ü	–	ü	ü[3, 4]
	Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin)	ü	ü[1, 2]	ü	ü[3, 4]
	Demyelinating disorders (including MS, GBS and optic neuritis)	ü	–	ü	ü[3, 4]
	Immune reactions (including lupus-like reactions and allergic reactions)	ü	–	ü	–
	Sarcoidosis	ü	–	ü	–
	CHF	ü	–	ü	ü[3, 4]
	MI	ü	–	ü	–
	CVA	ü	–	ü	–
	ILD	ü	–	ü	–
	Pulmonary embolism	ü	–	ü	–
	Cutaneous vasculitis	ü	–	ü	–
	SJS and erythema multiforme	ü	–	ü	–
	Worsening and new onset of PsO	ü	–	ü	–
	Haematologic disorders	ü	–	ü	–
	Intestinal perforation	ü	–	ü	–
	Liver failure and Other Liver Events	ü	–	ü	–
	Elevated ALT levels	ü	ü[1, 2]	ü	–
	Autoimmune Hepatitis	ü	ü[1, 2]	ü	–
	Medication errors and maladministration.	ü	–	–	–
Important potential risks	Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma)	ü	–	ü	ü[3, 4]
	Vasculitis (non-cutaneous)	ü	–	–	–
	PML	ü	–	–	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	RPLS	ü	–	–	–
	ALS	ü	–	–	–
	Infections in infants exposed to adalimumab in utero	ü	–	ü	–
	Off-label use	ü	–	–	–
Missing information	Subjects with immune-compromised conditions either due to underlying conditions (that is, diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications	ü	–	ü	–
	Pregnant and lactating women	ü	ü[1, 2]	ü	–

1) Prospective cohort study; 2) Rheumatic disease registry; 3) Patient alert card; 4) Educational program for healthcare professionals and patients; 5) EU specific safety concern

- Routine and additional pharmacovigilance activities have been proposed. Routine pharmacovigilance includes a pregnancy follow-up form.
- Routine and additional risk minimisation activities have been proposed. The safety monograph for healthcare professionals and patient brochure are materials for general user support rather than required additional risk minimisation activities that target specific safety concerns.

New and outstanding recommendations from conclusions from third round

The RMP is acceptable. The recommendations made in the second round evaluation, along with consideration of the sponsor response were provided.

There is one critical outstanding recommendation:

The Patient Alert Card should be revised to address the patient; rather than healthcare professionals; and to include additional safety concerns and more information to enable the patient to recognise important signs/symptoms and take appropriate action.

The sponsor has committed to developing and implementing the 'safety monograph' and 'Tuberculosis (TB) screening and checklist brochure for adalimumab' which are additional risk minimisation activities for Healthcare Professionals (HCP). As requested, these activities are listed in ASA version 3.0. However, these are for general user support rather than required additional risk minimisation activities for specific safety concerns.

The sponsor should focus on developing the patient directed risk minimisation tool, as this is considered important to ensure safe use.

Proposed 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 proposed wording for the conditions of registration are:

> Implement EU-RMP version 1.0 (dated 13 June 2016; DLP 1 December 2015) and ASA version 3.0 (dated 17 October 2017), which must be updated with revised patient-directed risk minimisation tools (see below), and any future updates as a condition of registration.
>
> The Patient Alert Card or an equivalent patient-directed risk minimisation tool must be implemented to the satisfaction of the TGA. Draft materials must be provided to the TGA for review prior to launch.

Other advice to the Delegate

The sponsor has amended the draft PI to address RMP recommendations to reduce off-label use, as follows:

> Indications; added 'Hadlima is indicated for treatment of rheumatoid arthritis in adults only.'
>
> Dosage and administration; added 'Hadlima is only available as 40 mg pre-filled syringe and 40 mg PushTouch auto-injector. It is not possible to administer less than a full 40 mg dose. If an alternate dose is required, other adalimumab products offering such an option should be used.'

VII. Overall conclusion and risk/benefit assessment

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

Background

This submission is to register a biosimilar version of adalimumab (Humira) under the product name Hadlima which was developed by Samsung Bioepis. In this submission, similarity to Humira (that is the reference medicinal product) is claimed. The application for Hadlima, also known as SB5, is requesting approval of only the rheumatoid arthritis (RA) indication in adults, that is approved for Humira, and not the other indications currently approved for Humira in Australia due to intellectual property reasons, that is not juvenile idiopathic arthritis (polyarticular and enthesitis-related), ankylosing spondylitis, psoriatic arthritis, psoriasis in adults and children, Crohn's disease in adults and children (≥ 6 years), ulcerative colitis, hidradenitis suppurativa in adults and adolescents (from 12 years of age) and uveitis. The sponsor is proposing a single strength of 40 mg solution for injection (pre-filled syringe and auto-injector) for registration (same strength as Humira) and the same dosing instructions as Humira for rheumatoid arthritis. The proposed PI is essentially the same as the Humira PI except for additional comparability data and the deletion of the pharmacology, clinical trials, immunogenicity, indications, precautions, adverse effects and dosage information related to the other indications approved for Humira.

The sponsor initially applied for all indications approved for Humira and with variations to the paediatric indications due to the absence of lower strengths of Hadlima that are currently approved for Humira, however during the evaluation process the sponsor

requested removal of these indications and related information in the PI, therefore only the rheumatoid arthritis indication in adults is now being requested.

The submission is clinically supported by a Phase III study comparing the efficacy and safety of Hadlima with Humira in RA patients for 52 weeks (including a one way switch from Humira to Hadlima) and a Phase I study providing pharmacokinetic and safety data in healthy volunteers. The submission is also supported by two additional clinical studies that relate to the auto-injector device. The development program for Hadlima was guided by the European Medicines Agency (EMA) and FDA requirements for biosimilar medicines. The reference drug, Humira, used in the Phase III study, was sourced from the EU and a bridging comparability exercise was undertaken with the Australian registered Humira. The pharmacokinetic study compared Hadlima with EU and US sourced Humira.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences that bind with high affinity and specificity to soluble human tumour necrosis factor (TNFα), but not lymphotoxin (TNFβ), thereby preventing the interaction between TNF, and the p55 and p75 cell surface TNF receptors. As a consequence, TNF is rendered biologically inactive.

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. It is the second most common form of arthritis and the most common autoimmune disease in Australia with a prevalence of 2%.

Hadlima has not been previously considered by ACM. Humira was first approved for RA in Australia in 2003.

Hadlima has been approved in Europe (Aug 2017) under the name Imraldi for the same indications as Humira in Europe and only as a 40 mg strength pre-filled syringe and not the auto-injector or other strengths available for Humira. It is under evaluation in Canada (submitted February 2017). In the USA, the application has not been filed due to the sponsor not being able to meet the FDAs request in time for a drug substance production schedule for the purpose of pre-licence inspection.[19] The approved indications in Europe are as follows:

Rheumatoid arthritis

Imraldi in combination with methotrexate, is indicated for:

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

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

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Imraldi in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had

[19] Clarification: Imraldi is now available in the auto-injector presentation in the EU, and that the product is now approved in Canada under the name Hadlima (Hadlima PFS and Hadlima PushTouch)

an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Imraldi can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

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

Ankylosing spondylitis (AS)

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

Axial spondyloarthritis

Axial spondyloarthritis without radiographic evidence of AS

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

Psoriatic arthritis

Imraldi is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

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

Paediatric plaque psoriasis

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

Hidradenitis suppurativa (HS)

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

Crohn's disease

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

Paediatric Crohn's disease

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

Ulcerative colitis

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

Uveitis

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

The TGA has produced a specific guideline in relation to biosimilar medicines, along with the adoption of numerous EU guidelines, which explains the background to biosimilars and regulatory aspects. The TGA published guideline is called 'Evaluation of biosimilars' which was published on 30 July 2013 and was updated in December 2015.[10] For details please see above in the Clinical section under Guidelines.

There are a number of specific clinical EU guideline adopted by the TGA relevant to this submission, besides the general guidelines (please see above in the Clinical section under Guidelines).

Quality

The quality evaluator has no objections on quality grounds to the approval of Hadlima provided outstanding GMP clearances are issued prior to registration and has recommended batch release testing as a condition of registration. The sponsor used EU sourced Humira as the reference product to demonstrate biosimilarity in terms of quality and non-clinical comparability exercises and in the clinical study, therefore a bridging comparability study was undertaken to compare EU and Australian sourced Humira. Extensive characterisation studies involving comparison of primary, secondary and tertiary structures, physicochemical properties and biological activities showed that Hadlima and EU Humira are generally similar, however some differences were noted. EU Humira was also found to be comparable to Australian Humira. The differences discussed by the evaluator were:

- Carbohydrate structure; %Afucose and %G0F
  - % Afucose level of Hadlima was slightly higher than that of the upper limit of the similarity range and % G0F levels of Hadlima were found to fall below the similarity range. These differences were shown to have no effect on FcγRIIIa binding and antibody dependent cell mediated cytotoxicity (ADCC) activities. All other glycan structure were shown to be in the similar range, therefore the differences were considered not significant.
- Purity and impurities
  - % Main of Hadlima batches were out of similarity range, which was attributed to the higher % non-glycosylated heavy chain (NGHC) level of Hadlima than that of EU Humira. The N-glycosylation at Fc region of antibodies is known to be associated with Fc-related functional activities. Considering the increase in %NGHC was shown to be above the reference product, and ADCC activity was shown to be within similarity range, the slight differences observed were not considered to have an impact on the biological activity. Therefore, the differences in %Main of Hadlima and EU Humira were not considered significant.
- Charge variants

– The relative contents of acidic variants in Hadlima were higher than the similarity range, whereas the relative content of the basic peak of Hadlima was lower than the similarity range. However, no differences in the molecular forms were observed in the charge variants of Hadlima and EU Humira and charge variant content did not affect biological activity including TNFα binding and ADCC. The observed differences in charge variants between Hadlima and EU Humira should not affect the apoptotic activity of Hadlima.

Sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Hadlima have been controlled to an acceptable level. There are no objections to the registration of this product from sterility; endotoxin, container safety and viral safety related aspects. A shelf life of 36 months when stored at 5 ± 3°C, protected from light, was supported by the data. The PI, CMI and labels from a quality perspective were acceptable.

Nonclinical

The nonclinical evaluator has no objections to the registration of Hadlima. The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat dose toxicity. The scope of the nonclinical program is in general accordance with the EMA guideline on nonclinical assessment of biological medicines.[12] Nonclinical in vivo studies only used US-Humira which was considered justified by the evaluator. There were no significant differences between Hadlima and US-Humira in the in vivo comparative pharmacology, pharmacokinetic and toxicity studies.

Clinical

The clinical dossier included the following data:

- 1 clinical pharmacology study (SB5-G11-NHV) in healthy volunteers that provided pharmacokinetic (PK), immunogenicity, tolerability and safety data.
- 1 clinical pharmacology trial (SB5-G12-NHV) in healthy volunteers that provided PK data and safety information on Hadlima given by either auto-injector device (AID) or pre-filled syringe (PFS).
- 1 open label trial (SB5-G21-RA) of Hadlima administered by PFS and AID in subjects with RA to compare injection site pain.
- 1 pivotal clinical study (SB5-G31-RA) in adult patients with active RA for 52 weeks, including a PK sub-study and switching data.

Pharmacokinetics

The clinical dossier presented three studies for demonstrating similarity in PK characteristics between Hadlima and Humira. EU Humira was used in the Phase I and III studies as the reference product.

Study SB5-G11-NHV

The first study, SB5-G11-NHV, was a single dose, randomised, single-blind, three-arm, parallel group, Phase I study conducted in 189 healthy subjects at a single centre comparing Hadlima, EU sourced Humira and US sourced Humira. All subjects received a 40 mg subcutaneous dose. A conventional cross-over design was not possible because of the long half-life of adalimumab. The primary PK variables (AUC_{inf} and C_{max} using 0.8 to 1.25 confidence limits), and secondary variables, were measured to compare Hadlima with

EU and US sourced adalimumab and to compare EU and US sourced Humira. The results for key variables are as follows:

1. Hadlima and EU Humira were comparable (ratio) for:
    a. AUC_{inf} (0.990, 90% CI 0.885 to 1.108)
    b. AUC_{last} (1.027, 90% CI 0.915 to 1.153)
    c. C_{max} (0.957, 90% CI 0.870 to 1.054)
2. Hadlima and US Humira were comparable
3. EU Humira and US Humira were also comparable.

Greater than 95% of all subjects tested positive for anti-drug antibodies (ADA) with neutralising antibodies (NAb) to adalimumab similar amongst the three groups (79.0% for Hadlima and 80.0% for EU Humira). For subjects with NAb positive results, AUC_{inf} values across the 3 groups were lower by about a third compared to Nab negative subjects, however C_{max} results were similar.

Study SB5-G12-NHV

Study, SB5-G12-NHV, was a single dose, randomised, open label, two arm, parallel group, Phase I study conducted in 190 healthy subjects comparing PK, tolerability and safety of Hadlima administered by PFS and AID. All but one of the randomised subjects of the SB5 PFS group received a 40 mg subcutaneous dose and primary PK variables (AUC_{inf}, AUC_{last} and C_{max} using 0.8 to 1.25 confidence limits), and secondary variables, were measured. The results for key variables showed the AID and PFS were comparable (ratio):

- AUC_{inf} (1.104, 90% CI 0.9953 to 1.2240)
- AUC_{last} (1.070, 90% CI 0.9802 to 1.1687)
- C_{max} (1.021, 90% CI 0.9503 to 1.0968)
- T_{max} was 168 hours for both
- $T_{1/2}$ mean 384.03 hours for AID and 320.48 hours for PFS
- Apparent drug clearance (CL/F) 17.4 mL/hours for AID and 19.25 mL/hours for PFS

SB5-G31-RA

Study SB5-G31-RA was a sub-study of the Phase III clinical study in rheumatoid arthritis. This sub study was conducted in 356 patients (178 Hadlima and 178 EU Humira) who provided baseline and trough levels. Steady state concentrations for Hadlima and Humira were achieved by 12 weeks of therapy. Mean serum trough concentrations of adalimumab were comparable between Hadlima (ranging from, 3.85 µg/mL at Week 4, to 6.76 µg/mL at Week 24) and EU Humira (ranging from 3.89 µg/mL at Week 4 to 6.77 µg/mL at Week 24). Both formulations of adalimumab exhibited high variability with the CV% ranging from 51.14 to 68.44% for Hadlima and 45.82 to 68.91% for EU Humira. There was no significant difference between the 2 treatment groups in ADA positivity (32.1% for Hadlima and 31.2% for Humira) however C_{trough} values were lower in both groups with positive ADA results compared to those who were ADA negative. Up to Week 52, ADA positivity occurred in 35.8% Hadlima versus 37.4% continuous Humira and 38.5% Humira switched to Hadlima switch group. The incidence of developing NAb at Week 52 was 50% Hadlima versus 54.7% overall Humira.

Pharmacodynamics

This submission did not contain any specific pharmacodynamic (PD) studies.

Efficacy

The dose selected for the pivotal study was based on the approved dose used in the Humira PI for RA.

Study SB5-G31-RA

Study SB5-G31-RA: This study was a 52 week, multinational, multicentre, randomised, double blind, parallel-group, equivalence trial of Hadlima versus EU Humira in 544 patients with moderate to severe rheumatoid arthritis, despite methotrexate (MTX) treatment. Patients were treated with 40 mg Hadlima or Humira every other week on a background of MTX. After 24 weeks patients on Humira were randomised to either continue Humira or switch to Hadlima until Week 50 (last dose). MTX at a dose of 10 to 25 mg weekly and folic acid were taken during the study. The study had approximately 80% power and an equivalence margin of ± 15%. To declare equivalence between the 2 treatment groups, the 2 sided 95% CI of the difference of the two populations should be contained within ± 15%. Study completion to Week 24 was high at 93.4% and at Week 52 was 96.3%. Major protocol deviations that led to exclusion from the respective analyses were slightly higher on Hadlima than Humira for the per-protocol set at Week 24 (7.7% versus 6.6%) and higher for the per-protocol set at Week 52 (15.1% versus 9.5%). At baseline, Hadlima versus Humira had comparable demographic and disease characteristics except for age (mean 49.8-52.5 years, 81% female, 99% White, mean 5.5 years of RA, mean approximately 15 mg of MTX at baseline with a mean 39.5 to 37.8 months prior use, mean 23.9 to 24.1 tender joints, mean 15.5 to 15.8 swollen joints, mean 11.47 to 12.64 mg/L CRP, mean 39.6 mm/hour ESR, 74.9 to 67.8% Rheumatoid factor positive, mean mTSS of 29.51 to 31.39 Sharp units).

The primary efficacy outcome using the validated ACR20 response at Week 24, per-protocol analysis, demonstrated equivalence at 72.4% Hadlima versus 72.2% Humira (treatment difference of 0.1%, 95% CI -7.83% to 8.13%); that is within the pre-specified equivalence margins. The full analysis set cohort using the non-responder analysis demonstrated similar findings as did two additional sensitivity analyses (68.0% Hadlima versus 67.4% Humira, treatment difference of 0.8%, 95% CI -7.03% to 8.56%). A time-response curve demonstrated similarity.

Secondary efficacy endpoints comparing Hadlima versus Humira (treatment difference, 95% CI) at Week 24 or Hadlima versus continuous Humira versus Humira ® Hadlima switch group at Week 52 were supportive:

- ACR20 at Week 52 (PPS2): 76.9% versus 71.2% versus 81.1%
  - The lower limits of the 95% CI of the adjusted treatment differences were within the equivalence margins of −15% to 15%; however, the upper limits were not. The adjusted treatment related difference using non-responder analysis in the FAS was within the equivalence margin.
- ACR20 at Week 52 (FAS): 77.8% versus 73.4% versus 78.8%
- ACR50 at Week 24 (PPS1): 38.1% versus 39.7% (−2.0%, −10.69%, 6.75%)
- ACR70 at Week 24 (PPS1): 19.2% versus 20.3% (−1.3%, −8.41%, 5.80%)
- ACR50 at Week 52 (PPS2): 49.1% versus 51.4% versus 53.8%
- ACR70 at Week 52 (PPS2): 31.1% versus 30.6% versus 26.4%
- ACR-N at Week 24: 40.17 versus 39.58 (0.4, 95% CI−4.61, 5.34)
- ACR-N at Week 52: 48.42 versus 46.14 versus 49.58
- DAS28 score change at Week 24: -2.74 versus -2.68 (−0.04, 95% CI −0.26, 0.17)
- DAS28 score change at Week 52: -3.05 versus -2.92 versus -3.02

- EULAR at Week 24: good was 34.1% versus 34.6%, moderate was 59.2% versus 58.8%
- EULAR at Week 52: good was 47.8% versus 46.0% versus 46.6%, moderate was 45.7% versus 45.2% versus 47.5%
- Major Clinical Response (ACR70 for 6 months) at Week 52: 15.7% versus 9.7% versus 15.3%
- Change from baseline in the mTSS at Week 52 (FAS): 0.17 units versus 0.50 versus 0.25
  - Change in joint erosions were similar between the groups but there was a slightly higher mean increase from baseline in the joint space narrowing score in the continuous Humira versus Hadlima groups.

At Weeks 24 and 52, the rates of ACR20, ACR50 and ACR70 response were similar between the 2 treatment groups among subjects who had negative ADA results but the ACR20 response rate at Week 24 was significantly lower on Hadlima (57.5%) versus Humira (71.2%) among subjects who had a positive ADA result (difference −17.5% (95% CI −33.3%, −1.8%)). However, ACR50 and ACR70 responses at Week 24 were similar between Hadlima and Humira in subjects with a positive ADA result up to Week 24: 28.8% versus 35.6% for ACR50, and 19.2% versus 16.4% for ACR70. In subjects with positive ADA, the ACR20 response rates at Week 52 remained lower on Hadlima at 67.1% versus 76.2% in the continuous Humira arm and 82.1% on Humira switched to Hadlima switch group. The sponsor provided a re-analysis of the data (CER, p88) that still showed a lower response for Hadlima versus Humira at Week 24 (ACR20: 50.7% versus 71.6%) but closer results at Week 52 (67.2% versus 72.5% versus 77.1% in the Hadlima versus continuous Humira versus Humira switched to Hadlima). There were no significant interactions in the ACR20 response rate at Week 24 between treatment and various factors including region (EU and non-EU), age group (< 65 years and ≥ 65 years), gender, race/ethnicity and baseline CRP level (≥ 10 mg/L and < 10 mg/L) although ACR20 response rates were somewhat higher for both adalimumab therapies in subjects with CRP readings > 10 mg/L at baseline.

Study SB5-G21-RA

Study SB5-G21-RA: This study was an open label, single arm, Phase II study conducted in 49 subjects with RA for 12 weeks to compare the usability and safety of the AID pen and PFS administration devices of Hadlima. All subjects received a 40 mg subcutaneous dose of Hadlima using the PFS for the first two doses and then the AID for the remaining 4 doses, every other week. The primary endpoint was a composite of the change in injection site pain score (immediately post-injection and between 15 to 30 minutes' post-injection) using an 11 point visual numeric scale from Week 2 to Week 6. Results demonstrated similarity between Hadlima via the PFS at Week 2 and via the AID pen at Week 6 for overall impression and pain scores and a higher preference for the AID device.

Safety

The following information is from the pivotal study unless noted otherwise.

The mean exposure up to Week 52 was 334 days on Hadlima with 216 exposed for ≥ 351 days. Treatment emergent adverse events (TEAEs) for Hadlima versus Humira occurred at similar frequencies in both groups up to Week 24 (35.8% versus 40.7%), except for nasopharyngitis being more frequent on Humira (4.9% versus 9.2%), with most TEAEs being mild to moderate severity. Injection site reactions were similar (3% versus 2.9%). The most frequent groups of adverse events were also similar between Hadlima and Humira: infections and infestations (17.2% versus 18.3%), musculoskeletal and connective tissue (7.5% versus 5.1%), nervous system (5.6% versus 3.7%), gastrointestinal (5.2% versus 5.5%), abnormal investigations (4.9% versus 6.2%) and

general disorders and administration site conditions (4.9% versus 5.9%). Up to Week 52, TEAEs for Hadlima versus continuous Humira was 52.2% versus 54.3% with similar but higher frequencies than up to Week 24, by system organ class. The most frequently occurring TEAEs across the three groups of Hadlima, continuous Humira and overall Humira) were nasopharyngitis (9.0 to 12.6%), headache (4.1 to 5.1%), bronchitis (3.9 to 4.1%), latent TB (2.9 to 5.5%), upper respiratory tract infection (0.8 to 3.7%), raised ALT values (3.4 to 5.5%), spinal pain (3.0 to 4.7%), urinary tract infection (1.6 to 3.0%), nausea (2.2 to 3.1%), back pain (1.5 to 2.6%) and increased AST (1.1 to 2.4%). Up to Week 52, injection site reaction frequencies were comparable between Hadlima and overall Humira and continuous Humira treatment groups. After Week 24, AEs by groups for Hadlima versus continuous Humira versus Humira switched to Hadlima were: infections and infestations (16.5% versus 14.2% versus 18.4%), musculoskeletal and connective tissue disorders (6.3% versus 6.3% versus 8.0%) and abnormal investigation results (3.5% versus 4.7% versus 7.2%). Of note were: latent TB (3.1% versus 5.5% versus 0.8%), Mycobacterium TB complex test positive (0.8% versus 0.8% versus 3.2%) and increased ALT values (1.2% versus 2.4% versus 0.8%).

Adverse drugs reactions occurred at an overall similar frequency up to Week 24 and Week 52, with injection site reactions and injection site erythema slightly higher on Humira at both times. At Week 52, subjects on Humira also had a slightly higher incidence of raised ALT values and latent TB compared to Hadlima. After Week 24, ADRs occurred in 7.9% Hadlima, 9.6% Humira switched to Hadlima and 9.4% continuous Humira groups. Latent TB was 0.8% Hadlima, 0 subjects Humira switched to Hadlima and 3.1% continuous Humira groups.

Two deaths occurred on Humira (nil on Hadlima) and were considered to be unrelated to adalimumab. Serious AEs up to Week 24 occurred in 1.1% (n = 3) Hadlima versus 2.9% (n = 8) Humira. Up to Week 52, SAEs occurred in 3.4% Hadlima versus 5.9% overall Humira versus 4.7% continuous Humira. Infections and infestations were the most common SAE group at both time periods. After Week 24, 3 additional treatment related SAEs were reported: retinal oedema (Hadlima), bronchopneumonia (Humira switched to Hadlima) and glioblastoma multiforme (Humira switched to Hadlima). Malignant neoplasms occurred in 2 on Humira (lymphoma and papillary thyroid cancer) and 1 on Humira switched to Hadlima switch (glioblastoma multiforme as above). Discontinuations due to AEs were low.

Up to Week 52, elevated ALT values occurred in 3.7% Hadlima, 5.5% continuous Humira and 6.4% Humira switched to Hadlima. There were no possible Hy's law cases. At Week 24, QuantiFERON Gold testing was positive in 3.7% Hadlima versus 3.3% Humira. At Week 24, latent TB occurred in 4.5% Hadlima versus 3.7% Humira. At Week 52, the QuantiFERON Gold test results were comparable between the treatment groups and 4.1% Hadlima versus 3.2% Humira switched to Hadlima versus 4.7% continuous Humira had latent TB. Low neutrophil counts up to Week 52 occurred in 1.9% Hadlima, 0.8% continuous Humira and 2.4% Humira switched to Hadlima groups.

The percentages of subjects who experienced any AE and the types of AEs most commonly reported were comparable between Hadlima and Humira in subjects who were negative or positive ADA at Week 24 and 52 (including the Humira switched to Hadlima group). In Study SB5-G11-NHV, 176 AEs were reported in 103 (54.5% of 189) ADA positive subjects compared to 3 AEs in 1 (0.5% of 189) ADA negative subjects.

In Study SB5-G11-NHV, TEAEs tended to be lower on EU Humira than Hadlima but similar to US sourced Humira. In Study SB5-G21-RA to assess the AID, TEAEs occurred in 12.2% after first dose of PFS versus 38.8% at any time after first dose of AID with most being nasopharyngitis, diarrhoea, sinusitis, URTI, rash and raised ALT. In Study SB5-G12-NHV, the incidence of TEAEs was comparable between the AID (68.4%) and PFS (60.6%) with no discernible differences between the groups. No deaths were reported in the supporting

studies and there were a small number of unrelated SAEs reported. One case of neutropenia on Hadlima led to discontinuation from Study SB5-G21-RA.

Clinical evaluator's recommendation (if applicable)

The clinical evaluator has recommended approval of Hadlima for the RA indication in adult patients. The evaluator provided the following recommendation:

> 'The submission provides evidence that Hadlima is therapeutically equivalent to Humira in improving the signs and symptoms, as well radiographic outcomes in adult patients with active RA that are inadequately responding to MTX. This target treatment population is consistent with the main approved RA treatment population for Humira. In terms of safety, the 2 formulations of adalimumab appear to be clinically equivalent for the incidence and type of clinically significant safety concerns. The Hadlima clinical study program shows a low incidence of injection site reactions, and comparable immunogenicity in RA patients treated with Hadlima compared to Humira. Moreover, the safety profile (incidence and type) of Hadlima is within historical expectations for Humira therapy in the target population.
>
> In the second round evaluation, the sponsor is no longer seeking registration for Hadlima in any of the other 8 approved treatment indications for Humira. The applicant states this is due to legal (patent) concerns. However, after the response, there is significant concern for the implications that the applicant is not providing alternative Hadlima presentations to the 40 mg/0.8 mL vial, which has the potential for prescribing and dispensing errors, as well as increases the risk of off label use occurring with the registration of 2 adalimumab formulations in Australia. This is compounded by the sponsor only seeking registration in 1 of the 9 approved Humira treatment indications.

The clinical evaluator recommended that approval of the sponsor's proposed registration for Hadlima be subject to regular periodic safety update reports.

Risk management plan

The Pharmacovigilance and Special Access Branch (PSAB) has accepted the EU Risk Management Plan for Hadlima (adalimumab), version 1.0, dated 13 June 2016 (data lock point 1 December 2015), with the Australian Specific Annex, version 3.0, dated 17 October 2017. The RMP must be updated with revised patient directed risk minimisation tools.

The proposed Summary of Safety Concerns and their pharmacovigilance and risk minimisation measures for Australia are summarised in Table 9 above.

The pharmacovigilance activities include: routine activities, patient registries, pregnancy notification and outcome report and follow up forms for malignancies.

The risk minimisation activities include: routine activities, patient alert card, safety monograph, dear healthcare professional letters and a TB screening and checklist brochure.

The sponsor is not proposing to conduct specific surveillance studies in Australia or an Australian registry but will be monitoring safety through two European registries (BIOBADASER) and (ARTIS) and routine pharmacovigilance.

There is one outstanding matter. The Patient Alert Card proposed by the sponsor should be revised to address the patient rather than healthcare professionals and to include additional safety concerns and more information to enable the patient to recognise

important signs/symptoms and take appropriate action. The draft Patient Alert Card or an equivalent patient directed risk minimisation tool is to be provided to the TGA for review prior to launch. The PI and CMI will be included as package inserts.

Risk-benefit analysis

Delegate's considerations

The sponsor is only applying for the rheumatoid arthritis indication that is approved for Humira and not the other indications approved for Humira:

> *Rheumatoid Arthritis*
>
> *Hadlima 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.*
>
> *Hadlima can be used alone or in combination with methotrexate*

Current indications approved for Humira:

Rheumatoid Arthritis

Humira 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.

Humira can be used alone or in combination with methotrexate.

Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis

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

Enthesitis-Related Arthritis

Humira 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

Humira 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

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

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

Humira 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 to infliximab.*

Ulcerative colitis

Humira 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

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

Humira 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 in Adults and Adolescents (from 12 years of age).

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in 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.

Dosage

The sponsor is applying for the same dosage as Humira for rheumatoid arthritis and is not including the other dosage regimens in the PI for the other approved Humira indications:

Rheumatoid Arthritis

> The recommended dose of Hadlima for adult patients with rheumatoid arthritis is 40 mg administered fortnightly as a single dose. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics may be continued during treatment with Hadlima.
>
> Some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of Hadlima to 40 mg every week.

Preparation of Hadlima

> Hadlima is intended for use under the guidance and supervision of a physician. Patients may self-inject Hadlima if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.
>
> Sites for self-injection include thigh or abdomen. Injection sites should be rotated. New injections should never be given into areas where the skin is tender, bruised, red or hard.
>
> Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.
>
> Hadlima should not be mixed in the same syringe with any other medicine. Any unused product or waste material should be disposed of in accordance with local requirements.

Hadlima contains no antimicrobial agent. Hadlima is for single use in one patient only. Discard any residue.

Quality and nonclinical

The quality evaluator has no objections on quality grounds to the approval of Hadlima pending outstanding GMP clearances. Acceptable comparability on quality grounds was demonstrated between EU Humira and Hadlima and between EU Humira and Australian Humira, however some differences were noted in quality attributes which were not considered to have a significant effect. Whether these differences have clinical implications is unclear from the clinical data.

The nonclinical dossier was acceptable and the evaluator has no objections to registration.

Clinical

Pharmacology

Hadlima demonstrated comparable pharmacokinetics to EU Humira in healthy volunteers using $AUC_{inf,}$ AUC_{last} and C_{max}. In the sub study of the Phase III study in RA, similar trough adalimumab concentrations were seen with steady state by Week 12 but there was high variability. A study comparing the AID and PFS showed similar PK parameters. All 3 of the studies showed mean serum concentration time profile data consistent with the known PK characteristics of adalimumab. No specific pharmacodynamic studies were submitted which is acceptable given the established use of adalimumab and the clinical data.

Efficacy

The efficacy of Hadlima is supported by a single therapeutic equivalence study comparing it with EU Humira in a rheumatoid arthritis population taking a stable dose of methotrexate. Hadlima demonstrated equivalence to Humira for the primary endpoint and was supported by several secondary endpoints, consistent with the EU guideline on rheumatoid arthritis, up to Week 52. Patients in the study had established radiographic damage which was significantly higher than that expected in an Australian population but comparable between the groups in the study at baseline. The average dose of MTX used was similar to other biological DMARD studies but may represent sub-optimal dosing in clinical practice. The use of prior MTX in the study, as well as the measures of disease activity, is consistent with the approved RA indication for Humira which allows for combination therapy. The equivalence margin chosen in this study allowed for up to a 15% difference in efficacy but is considered to be the maximal acceptable margin and was the same margin used in other anti-TNF biosimilar studies. The selected efficacy endpoints are accepted validated measures that have been used in previous RA studies and are consistent with the EU guideline. Of note, the primary endpoint results were slightly higher in both groups than that reported for other adalimumab studies and other anti-TNF medicines however this is not a significant issue. The study comparing the PFS and AID demonstrated similar injection site pain scores and a higher preference for the AID.

The clinical evaluator had concerns about the external validity of the Phase III study to clinical practice in Australia (for example low dose weekly MTX as their sole prior DMARD treatment and about one fifth had taken MTX with 1 other conventional DMARD). However the evaluator noted that the study population meets the minimum criteria for prior DMARD therapy which is consistent with the proposed RA treatment indication for adalimumab.

Monotherapy and MTX naïve patients

The RA indication also allows use of adalimumab as monotherapy and in MTX naïve patients however the clinical study only used concomitant MTX in a population previously using MTX. It is not known if there would be differences in clinical effect without MTX. Methotrexate can alter the immunogenicity and pharmacokinetic profile of adalimumab.

Other strengths and dosage regimen

The sponsor is only requesting a 40 mg strength however Humira is also registered in strengths of 10 mg and 20 mg. Since the only dose for RA is 40 mg and is proposed in a PFS and AID, then the lack of these other strengths is not of significant concern for this application. The RA indication is also approved for a dose frequency of 40 mg weekly whereas the clinical study was conducted with a dose frequency of fortnightly only. Although there is no data with this dose frequency, a similar effect to Humira is expected given the biosimilarity demonstrated.

Safety

The safety profile of Hadlima was overall comparable to EU Humira from the pivotal study with an adequate sample size and duration of exposure that is consistent with the EU guideline on rheumatoid arthritis. Overall, the incidence of AEs, SAEs and discontinuations due to AEs were similar between groups. Infection related AEs were the most common with a similar frequency on both treatments. No deaths were reported in the Hadlima group. AEs were comparable between Hadlima and Humira in subjects with negative and positive ADA status. AEs in the supporting studies did not reveal significant concerns. The submitted data is limited to 60 weeks of follow-up therefore it will be important for the sponsor to collect data as part of pharmacovigilance.

Extrapolation of indications

In the submission, the sponsor provided a literature review of the evidence supporting extrapolation of treatment indications for the other approved adalimumab indications of Humira, however requested that only the rheumatoid arthritis indication was to be considered for Hadlima. The clinical evaluator has provided a review of the sponsor's information to support the extrapolation of indications however this is not relevant to the current application since no other indications are being requested. Only having the rheumatoid arthritis indication raises the possibility of off-label use for Hadlima. The sponsor is requested to outline how they intend to communicate to prescribers and pharmacists that Hadlima is only approved for RA and is only available as a 40 mg strength.

Immunogenicity

There is a potential for diminished clinical efficacy if a patient develops medium to high titres of ADA as this has been shown to reduce trough drug levels. The incidence of ADA development was very high in the PK study at > 95% across all groups and in the clinical study the overall incidences of positive ADA results at Weeks 24 (31.2 to 32.1%) and 52 (36.0 to 37.4%) were lower but similar across the groups. In the PK study, the incidence of Nab was high for Hadlima (comparable to Humira) but was lower in Study SB5-G31-RA. The differences between the studies may be due to concomitant MTX. The ACR responses for the Phase III study were similar between the two treatment groups among subjects who were ADA negative. However for subjects, who were ADA positive, the ACR20 response rate at Week 24 was significantly lower on Hadlima than Humira, but ACR50 and 70 results were more similar. At Week 52, the ACR20 response rates were more similar. The evaluator considers that the totality of the data shows that there isn't a clinically significant difference in efficacy for ADA positive patients treated with Hadlima compared with those given Humira. The difference was mostly seen at Week 24 and other time points were more comparable.

RMP

An acceptable RMP with ASA has been provided however the sponsor must update the patient alert card or equivalent patient directed risk minimisation tool.

Summary

Overall

The quality, nonclinical and clinical evaluators have all recommended approval and an acceptable RMP/ASA has been provided. Pending further advice from ACM, the Delegate considers that sufficient data and justification have been provided, consistent with adopted EU guidelines, to support the similarity of Hadlima to Australian Humira and to support the registration of Hadlima on quality, safety and efficacy grounds for the rheumatoid arthritis indication that is approved for Humira.

Switching

There is limited information about the safety and efficacy of switching from Humira to Hadlima and there is no data on the reverse switching or multiple switching between different formulations of adalimumab. The evaluator commented that there are at least theoretical concerns that such practice may increase the rates of immunogenicity.

The TGA biosimilars guideline does not require general switching precautions in the PIs of biosimilars. The adalimumab PI will include safety data (as well as efficacy data) on switching patients compared to those who stayed on Humira. The PI will also include data on ADA development. The PI advises that Hadlima is intended for use under the guidance and supervision of a physician and patients may self-inject if their physician determines it is appropriate and with proper training.

Data deficiencies

Efficacy data from an adalimumab monotherapy study (that is no concomitant MTX) is lacking and there is no data in a methotrexate naïve population as per the approved indication. Data beyond one year is not available. There is also no data using a dose frequency of 40 mg weekly and there is limited switching data and no multiple switching data. Hadlima has not been studied in patients with significant organ dysfunction or those at high risk of infection.

Conditions of registration

The following are proposed as conditions of registration and the sponsor is invited to comment in the Pre-ACM response:

1. The implementation in Australia of the EU Risk Management Plan for Hadlima (adalimumab), version 1.0, dated 13 June 2016 (data lock point 1 December 2015), with the Australian Specific Annex, version 3.0, dated 17 October 2017, which must be updated with revised patient-directed risk minimisation tools (see below), included with submission PM-2016-03547-1-3, and any subsequent revisions, as agreed with the TGA.
2. The Patient Alert Card or an equivalent patient-directed risk minimisation tool must be implemented to the satisfaction of the TGA. Draft materials must be provided to the TGA for review prior to launch.
3. Batch Release Testing
    a. It is a condition of registration that all batches of Hadlima adalimumab (rch) imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
    b. It is a condition of registration that each batch of Hadlima adalimumab (rch) imported into 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:

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

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

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

iv. Five 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.

Arrangement for delivery of the requested items can be made by contacting Biochemistry.Testing@tga.gov.au.

Samples and data should be forwarded to the Laboratories Branch, Biochemistry Section, before release of each batch and with sufficient lead time to allow for testing. The address for courier delivery is:

Laboratories Branch – Biochemistry

Therapeutic Goods Administration

136 Narrabundah Lane

Symonston, ACT 2609

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

c. Compliance with Certified Product Details (CPD): The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACM Response:

1. Provide an update on the outstanding GMP clearances.
2. Comment on the potential clinical implications of each of the differences noted in the comparability exercise between Hadlima and Humira, as discussed above in the quality evaluation.
3. Are any further studies planned to investigate the efficacy and safety of Hadlima including any switching studies?
4. Please summarise what actions are proposed by the sponsor to inform prescribers and pharmacists that Hadlima is only approved for rheumatoid arthritis and is only available as a 40 mg strength.

Summary of issues

The primary issues with this submission are as follows:

1. The efficacy data overall demonstrated comparability between Hadlima and Humira.

2. The safety profiles overall appeared to be comparable between Hadlima and Humira.
3. Anti-drug antibodies (ADA) developed at a similar frequency on both Hadlima and Humira in the clinical study. In ADA negative patients, ACR response rates were similar on Hadlima and Humira however in ADA positive patients there were some differences in ACR response rates. Immunogenicity may also be potentially different when concomitant methotrexate is not used.
4. The sponsor is applying for a single strength of adalimumab, 40 mg, which is approved for Humira and only one indication, rheumatoid arthritis, which is approved for Humira. As such, the product information proposed has removed the pharmacology, clinical trials, immunogenicity, indications, precautions, adverse effects and dosage information related to the other indications approved for Humira.

The quality evaluator noted some minor differences between Hadlima and Humira in the comparability analyses.

Proposed action

The Delegate had no reason to say, at this time, that the application for Hadlima should not be approved for registration, pending further advice from ACM.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. What are ACMs views on the similarity of efficacy between Hadlima and Humira to support the rheumatoid arthritis indication for this biosimilar adalimumab?
2. What are ACMs views on the comparability of the safety profiles of Hadlima and Humira?
3. What are ACMs views on the differences noted in ACR response rates in ADA positive patients on Hadlima compared with Humira?
4. What are ACMs views on the presentation of the product information, given the sponsor is only requesting the rheumatoid arthritis indication, especially in relation to exclusion of safety information related to the other indications, for example immunogenicity, precautions and adverse effects?
5. What are ACMs views on the clinical significance of the differences noted in the quality comparability analyses?

The committee is also 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

Response to questions from Delegate

Response to question 1

Provide an update on the outstanding GMP clearances: As noted, there are outstanding GMP clearances that are currently under review and are expected to be resolved.

Response to Question 2

Comment on the potential clinical implications of each of the differences noted in the comparability exercise between Hadlima and Humira, as discussed above in the quality evaluation: As the Agency commented, minor differences in some quality attributes were observed between Hadlima and Humira for the physicochemical properties. The potential

clinical implication of the differences between Hadlima and Humira is discussed in depth as follows.

- Carbohydrate Structure; % Afucose and % G0F

  The level of %Afucose was slightly higher in Hadlima than that of Humira. However, FcγRIIIa binding and ADCC activities, which are known to be affected by the %Afucose level, of Hadlima and Humira were similar. In terms of immunogenicity, exogenous antigens generally tend to induce immunogenicity. However, afucosylated glycans such as G0, G1/G1', and G2 and high mannosylated glycans such as M5-M9 are endogenously expressed in humans and are also observed in Humira. This indicates that a negative impact on immunogenicity is not foreseen.[20] The scientific literature and the clinical data support that %Afucose would not significantly influence ADCC and other important biological properties in Hadlima and Humira.

  The level of %G0F was slightly lower in Hadlima than that of Humira. The applicant investigated two physiological properties that might potentially be affected by G0F levels: pharmacokinetics (PK) and immunogenicity. With respect to PK, Hadlima and Humira showed similar FcRn binding activities, and similar PK profiles in non-clinical (PK in cynomolgus monkeys) and clinical studies. With respect to immunogenicity, the abundance (approximately 23%) of the G0F glycoform among natural human IgGs suggests that this glycoform would not be immunogenic.[21] The scientific literature and the clinical data support that %G0F would not significantly influence ADCC and other important biological properties in Hadlima and Humira.

  Therefore, the slight difference in % Afucose and % G0F are not considered to have an impact on the biological activity and to be translated into clinically meaningful difference

- Purity and Impurities; % Main and % NGHC

  %Main (%HC + %LC) of Hadlima analysed was slightly lower in Hadlima than that of Humira, which was attributed to the higher level of NGHC of Hadlima. However, it is known that the absence of glycan at Asn_{301}, resulting in unmasking of the region, is not related to immunogenicity.[22] In order to justify the difference between Hadlima and Humira, the applicant provided experimental data demonstrating that the NGHC levels detected in Hadlima will not impact on FcRn binding, TNFα binding, and FcγRIIIa binding nor on ADCC activity. Furthermore, the results from an orthogonal analysis showed that %IgG was similar between Hadlima and Humira. Therefore, the slight differences observed in %Main are not considered to be significant and to be translated into clinically meaningful difference.

- Charge Variants; % Acidic and % Basic

  Charge variants in Hadlima and Humira were evaluated. Overall, both assessments showed that Hadlima was found to possess a higher content of acidic variants and a lower content of basic variants, compared to those of Humira.

  In order to rule out the residual uncertainty on the differences, acidic and basic variants were, and the impact on TNFα binding and ADCC activities was assessed. In addition, comparative studies using sialidase A or carboxypeptidase B treated Hadlima and Humira samples were conducted. These results show that the differences in

[20] Jefferis, R 2005 CCE IX: Review Glycosylation of Recombinant Antibody Therapeutics. *Biotechnol. Prog.* 2005, 21, 11-16
[21] Farooq M et al. 1997 EGC1 Glycosylation of polyclonal and paraprotein lgG in multiple myeloma. *Glycoconjugate Journal* 1997; 14: 489-492
[22] Jung ST et al, 2011 Bypassing glycosylation: engineering aglycosylated full-length IgG antibodies for human therapy *Current Opinion in Biotechnology* 2011; 22: 858–867

charged variants are mainly caused by the difference in C-terminal variants, as well as the difference in the content of sialylated N-glycans. The differences in charge variant between Hadlima and Humira were investigated across the fractions with regards to TNF-α binding, ADCC, FcRn binding, and complement-dependent cytotoxicity (CDC) activities. The results showed that the difference in charge variants would have no impact on these biological activities. Based on the results from identity and biological activity studies conducted using fractionated samples, it can be concluded that the minor difference in charge variants are not considered to be significant and to be translated into clinically meaningful difference.

Therefore, based on the assessment discussed above, the applicant concludes that the observed minor differences in some quality attributes are considered non-significant, and do not translate into clinical outcomes.

Response to Question 3

Are any further studies planned to investigate the efficacy and safety of Hadlima including any switching studies?: The Study SB5-G31-RA already included a switching design and its result clearly showed that the comparable efficacy was maintained after switching and there were no clinical meaningful differences in safety profiles in patients who switched from Humira to Hadlima. Therefore, the applicant does not plan to conduct any further clinical studies investigating the efficacy and safety of Hadlima including any switch studies.

Response to Question 4

Please summarise what actions are proposed by the sponsor to inform prescribers and pharmacists that Hadlima is only approved for rheumatoid arthritis and is only available as a 40 mg strength.: To inform prescribers and pharmacists that Hadlima is only approved for rheumatoid arthritis and is only available as a 40 mg strength, the Applicant included the following statement under Section 'Dosage and Administration' of the PI:

- Hadlima is indicated for treatment of rheumatoid arthritis in adults only.
- Hadlima is only available as 40 mg pre-filled syringe and 40 mg PushTouch auto-injector.

In addition, the following statement has also been included in each Section 'immunogenicity', 'precautions', and 'adverse effects' of the PI in accordance with the TGA's request:

> Hadlima is indicated for treatment of rheumatoid arthritis in adults only. Available safety information for adalimumab treatment in Juvenile Idiopathic Arthritis (Polyarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis), Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease in Adults and Children, Ulcerative colitis, Psoriasis in Adults and Children, Hidradenitis Suppurativa in Adults and Adolescents, and Uveitis is also summarised in this section.

Advisory committee considerations[23]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Hadlima solution for injection in pre-filled syringe and solution for injection in PushTouch auto-injector containing 40 mg of adalimumab to have an overall positive benefit-risk profile for the indication:

> *Rheumatoid Arthritis*
>
> *Hadlima 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.*
>
> *Hadlima can be used alone or in combination with methotrexate*

In making this recommendation the ACM:

- noted the sponsor has only applied for the rheumatoid arthritis indication and not the other indications approved for Humira.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information / Consumer Medicine Information amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

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

1. What are ACMs views on the similarity of efficacy between Hadlima and Humira to support the rheumatoid arthritis indication for this biosimilar adalimumab?

The ACM agreed that there are no significant differences in clinical efficacy between Hadlima and Humira.

2. What are ACMs views on the comparability of the safety profiles of Hadlima and Humira?

The ACM was of the view that the safety profiles of Hadlima and Humira were comparable. The safety profiles for the Hadlima and Humira reported during the pivotal study (Study SB5-G31-RA) were very similar.

[23] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

3. What are ACMs views on the differences noted in ACR response rates in ADA positive patients on Hadlima compared with Humira?

The ACM noted the substantial difference in the ACR response rates in the ADA positive patients on Hadlima when compared with Humira in the ACR20 group. The difference was smaller in the ACR 50 group and there was no difference in the ACR 70 group. Approximately one-third of patients developed ADA at Week 24 in both treatment arms. The PI should adequately cover this issue.

4. What are ACMs views on the presentation of the product information, given the sponsor is only requesting the rheumatoid arthritis indication, especially in relation to exclusion of safety information related to the other indications, for example immunogenicity, precautions and adverse effects?

The ACM recommends the inclusion of all safety data, including safety data relating to the other indications not applied for by the sponsor, to be included in the PI.

5. What are ACMs views on the clinical significance of the differences noted in the quality module comparability analyses?

The ACM considered the differences raised by the quality module comparability analyses and was of the view that they are acceptable.

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 these products

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Hadlima adalimumab 40 mg solution for injection in syringe or auto-injector indicated for:

> *Rheumatoid Arthritis*
>
> *Hadlima 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.*
>
> *Hadlima can be used alone or in combination with methotrexate.*

Specific conditions of registration applying to these goods

- The Hadlima EU-Risk Management Plan (EU-RMP), version 1.2, dated 11 May 2017 (data lock point 1 December 2015), with Australian Specific Annex (version 3.0, dated 17 October 2017) , which must be updated with revised patient-directed additional risk minimisation tools (see below) included with submission PM-2016-03457-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The Patient Alert Card must be implemented to the satisfaction of the TGA. Draft materials must be provided to the TGA for review prior to supply.
- Batch Release Testing
  - It is a condition of registration that all batches of Hadlima adalimumab (rch) imported into 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 Hadlima adalimumab (rch) imported into 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.

- Compliance with Certified Product Details (CPD): The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) <https://www.tga.gov.au/guidance-7-certified-product-details>, in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The PI for Hadlima 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>.

Therapeutic Goods Administration

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