Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Ustekinumab

## Proprietary Product Name: Stelara

## Sponsor: Janssen-Cilag Pty Ltd

**July 2015**

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 Record (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, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

**List of the most common abbreviations used in this AusPAR 5**

**I. Introduction to product submission 8**

Submission details 8

Product background 8

Regulatory status 9

Product Information 10

**II. Quality findings 10**

**III. Nonclinical findings 10**

**IV. Clinical findings 11**

Introduction 11

Pharmacokinetics 14

Pharmacodynamics 15

Dosage selection for the pivotal studies 15

Efficacy 16

Safety 18

First round benefit-risk assessment 23

First round recommendation regarding authorisation 24

Clinical questions 25

Pharmacodynamics 25

Efficacy 25

Safety 25

Second round evaluation of clinical data submitted in response to questions 26

Second round benefit-risk assessment 29

Second round recommendation regarding authorisation 29

**V. Pharmacovigilance findings 30**

Risk management plan 30

**VI. Overall conclusion and risk/benefit assessment 36**

Quality 36

Nonclinical 36

Clinical 36

Risk management plan 46

Risk-benefit analysis 46

Outcome 55

**Attachment 1. Product Information 55**

**Attachment 2. Extract from the Clinical Evaluation Report 55**

# List of the most common abbreviations used in this AusPAR

| Abbreviation | Meaning |
|---|---|
| ACR | American College of Rheumatology |
| ADA | Anti-Drug Antibody |
| AE | Adverse Event |
| AS | Ankylosing Spondylitis |
| ANCOVA | Analysis of Covariance |
| BASDAI | Bath Ankylosing Spondylitis Disease Activity Index |
| BLQ | Below Level of Quantification |
| BMI | Body Mass Index |
| CASPAR | Classification Criteria for Psoriatic Arthritis |
| CI | Confidence interval |
| CL/F | Apparent Clearance |
| CMH | Cochran-Mantel-Haenszel |
| CRP | C-Reactive Protein |
| CS | Corticosteroids |
| CV | Coefficient of Variation |
| DLQI | Dermatology Life Quality Index |
| DMARD | Disease Modifying Anti-Rheumatic Drug |
| ECLIA | Electrochemiluminescent Immunoassay |
| ES | Erosion Score |
| ESR | Erythrocyte Sedimentation Ratio |
| GCP | Good Clinical Practice |
| HAQ-DI | Health Assessment Questionnaire – Disability Index |
| IL | Interleukin |
| JSN | Joint Space Narrowing |

| Abbreviation | Meaning |
|---|---|
| LEF | Leflunomide |
| LS | Least Square |
| MASES | Maastricht Ankylosing Spondylitis Enthesitis Score |
| MCID | Minimal Clinically Important Difference |
| MTX | Methotrexate |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| PASI | Psoriasis Area Severity Index |
| PD | Pharmacodynamic |
| PhGADA | Physician Global Assessment of Disease Activity |
| PK | Pharmacokinetic |
| PsA | Psoriatic Arthritis |
| PT | Preferred Term |
| PtGADA | Patient Global Assessment of Disease Activity |
| PY | Patient-Years |
| QOL | Quality of Life |
| q12w | Every 12 weeks |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SpA | Spondyloarthritis |
| SSZ | Sulfasalazine |
| TNF | Tumour Necrosis Factor |
| ULN | Upper Limit of Normal |
| USK | Ustekinumab |
| vdH-S | van der Heijde-Sharp score (modified for PsA) |

| Abbreviation | Meaning |
|---|---|
| V/F | Apparent Volume of Distribution |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | Extension of indication to include Psoriatic Arthritis |
| *Decision*: | Approved |
| *Date of decision:* | 9 February 2015 |
| *Active ingredient:* | Ustekinumab |
| *Product name:* | Stelara |
| *Sponsor's name and address:* | Janssen-Cilag Pty Ltd<br>Locked Bag 2070<br>North Ryde NSW 1670 |
| *Dose form:* | Solution for injection |
| *Strengths:* | 45 mg/0.5mL and 90 mg/1.0mL |
| *Containers:* | Injection vial or Pre-filled syringe |
| *Pack size:* | 1's |
| *Approved therapeutic use:* | *Psoriatic Arthritis (PsA)*<br><br>*Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) where response to previous non-biological DMARD therapy has been inadequate*. |
| *Routes of administration:* | Subcutaneous (SC) |
| *Dosage:* | *Psoriatic Arthritis*<br><br>*The recommended dose of Stelara is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Some patients with a body weight greater than 100 kg received a 90 mg dose in clinical trials and observed a clinical benefit. Treatment should be discontinued in patients who have shown no response after 28 weeks of treatment.* |
| *ARTG number (s):* | 149549, 149550, 165953 and 165954 |

## Product background

This AusPAR describes the application by the sponsor, Janssen-Cilag Pty Ltd, to extend the indications for Stelara (ustekinumab) to include psoriatic arthritis (PsA) as follows:

> *Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms, including the inhibition of structural damage, of active psoriatic arthritis in adult patients (18 years or older).*

Stelara is currently approved for use in the therapeutic indication of moderate to severe psoriasis.

PsA is a chronic inflammatory arthritis associated with skin psoriasis, which affects the joints, soft tissues (enthesitis and dactylitis) and skin. All of the disease manifestations may affect functional capacity and quality of life (QOL) of the patient. It is a multifaceted and heterogeneous disease which typically onsets between the ages of 30 and 55 years and affects men and women equally.

Skin psoriasis has prevalence of 2 to 3% in general population and approximately 30% patients with skin psoriasis develop PsA.[1] It is a complex disorder, characterised by inflammation, increased keratinocyte hyperproliferation and an altered epidermal differentiation population. Substantial evidence exists indicating that T-lymphocytes, macrophages and certain cytokines play a major role in the pathogenesis of the disease.

Ustekinumab (USK) is a first-in-class fully human immunoglobulin G1kappa (IgG1kappa) monoclonal antibody produced in a murine myeloma cell line using recombinant deoxyribonucleic acid (DNA) technology.

USK binds to p40 protein subunit of the human cytokines interleukin (IL) 12 and 23, preventing these cytokines from binding to IL-12R beta-1 receptor on the surface of immune cells. USK cannot bind to IL-12 or IL-23 when these are bound to IL-12 beta1 cell surface receptors. By binding to the shared p40 subunit of IL-12 and IL-23, USK may exert its clinical effects in both psoriasis and psoriatic arthritis through interruption of the T helper cell[2] (Th1 and Th17) cytokine pathways which are central to the pathology of these diseases. It is thought that IL-12 induces proliferation of naïve T-cell populations and that IL-23 is stimulatory to memory T-cell populations. The currently approved drugs for PsA include non-biological disease-modifying antirheumatic drugs (DMARDs; methotrexate (MTX), sulfasalazine and leflunomide) and several biologic DMARDs (anakinra, adalimumab, etanercept, infliximab, certlizumab and golimumab).

USK is proposed for first line use in Australia unlike the second line approval in the European Union (EU) (see *Regulatory status* below for details). The structural claim proposed in Australia is not included in either EU or the USA indications (see below *Regulatory status*), whereas use as monotherapy or in combination with MTX is common to all jurisdictions.

The proposed dosage for use in PsA is modelled on the currently approved dosing regimen in plaque psoriasis, that is, 45 mg subcutaneous (SC) loading doses at Weeks 0 and 4 followed by once every 12 weeks (q12w). In patients with body weight >100 kg, an alternative a higher dose (90 mg at Weeks 0 and 4 followed by q12w) is also proposed.

The relevant regulatory guideline is the TGA adopted EU document CHMP/EWP/438/04 *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis*.

This application was primarily based on supporting clinical data and the Risk Management Plan (RMP).

## Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 15 July 2009.

[1] Mease PJ. Psoriatic Arthritis: update on pathophysiology, assessment and management. Ann Rheum Dis 2011; 70: i77-i84.

[2] The T helper cells ($T_h$ cells) are a type of T cell that play an important role in the immune system, particularly in the adaptive immune system. They help the activity of other immune cells by releasing T cell cytokines. These cells help suppress or regulate immune responses.

Stelara is currently approved in Australia in adult patients with moderate to severe plaque psoriasis as follows:

> *Stelara is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.*

At the time the TGA considered this application similar applications had been approved in the EU, the USA and Singapore and was under consideration in Switzerland and New Zealand (Table 1).

**Table 1: International regulatory status**

| Country | Approval date |
|---|---|
| EU (centralised) | 19 September 2013 |
| US | 20 September 2013 |
| Canada | 21 January 2014 |
| Switzerland | Pending |
| New Zealand | Pending |
| Singapore | 25 September 2014 |

The PsA indication has been approved in EU as follows:

> *Stelara, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological DMARD therapy has been inadequate.*

The PsA indication has been approved in the USA as follows:

> *Stelara is indicated for the treatment of adult patients (18 years or older) with active psoriatic arthritis. Stelara can be used alone or in combination with MTX.*

### Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

# II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

# III. Nonclinical findings

In support of the proposed changes in the Pharmacology: Mechanism of action section of the Product Information, the sponsor has submitted 3 peer-reviewed published articles.

The literature submitted by the sponsor supports the statement that IL-23 responsive T-cells have been found in the entheses in a mouse model of arthritis, where IL-23 also

drives entheseal inflammation.[3] Furthermore, two articles submitted[4,5] provide evidence that implicates IL-23 and downstream pathways in bone erosion and destruction through up-regulation of receptor activator of nuclear factor k-B ligand (RANKL), which activates osteoclasts. Other published peer reviewed articles[6,7,8,9] provide support to the proposed statements in the PI.

# IV. Clinical findings

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

### Introduction

The submission contains 2 pivotal Phase III controlled trials (PSUMMIT I and PSUMMIT II) for the requested extension of indication to include the treatment of PsA. The 2 pivotal studies were designed with similar schema, eligibility criteria as well as doses and regimens of therapy so that the potential effect of USK on structural damage (as assessed by serial radiographs) could be evaluated from a pooled analysis at 24 and 52 weeks of treatment follow-up. However, the 2 studies were designed to independently evaluate the effect of USK on PsA signs and symptoms, physical function and health related quality of life (QOL). For both pivotal studies, the 24 week study reports provided in this submission were intended to provide the principal efficacy data supporting the indication of treating the signs and symptoms of PsA. However, the 52 week report for the PSUMMIT I trial, and the data collected up to Week 60 in PSUMMIT II were intended to complement the dataset for evaluating clinical efficacy and safety.

The sponsor has also submitted a single, placebo controlled Phase II study (C0743T10) in adult patients with PsA as supportive evidence. In this trial, patients were randomised to receive either placebo or USK 90 mg by subcutaneous injection at Weeks 0, 1, 2 and 3. At Week 12, subjects randomised to placebo were to receive USK 90 mg at Weeks 12 and 16.

USK is currently approved for the treatment of moderate to severe plaque psoriasis in adult patients under the registered trade name of Stelara. The sponsor does not propose a different registered drug name for this indication. Furthermore, no change in the drug formulation or presentation is proposed. USK has the Anatomical Therapeutic Chemical (ATC) code L04AC05, which relates to immunosuppressant drugs in the subclass of Interleukin inhibitors.

The sponsor proposes changes to the *Pharmacology, Clinical Trials, Precautions, Adverse Effects,* and *Dosage and Administration* sections of the PI, principally using the data obtained from the 2 pivotal studies. Comments on the proposed PI changes are beyond the scope of this AusPAR.

[3] Sherlock JP et al. IL-23 induces spondyloarthropathy by acting on ROR-gt+ CD3+CD4- CD8- entheseal resident T cells. Nature Med, 2012; 18(7): 1069-1077

[4] Adamopoulos JE et al. IL-23 is critical for induction of arthritis, osteoclast formation, and maintenance of bone mass. J Imm 2011; 187: 951-959.

[5] Sherlock JP et al. IL-23 induces spondyloarthropathy by acting on ROR-gt+ CD3+CD4- CD8- entheseal resident T cells. Nature Med, 2012; 18(7): 1069-1077.

[6] Germann T. and Rude E. Interleukin-12. *Int Arch Allergy Immunol* 1995, 108(2):103-12.

[7] Kurzeja M., Rudnicka L. and Olszewska M. New interleukin-23 pathway inhibitors in dermatology: ustekinumab, briakinumab, and secukinumab. *Am J Clin Dermatol* 2011, 12(2):113-25.

[8] Levine A.A. and Gottlieb A.B. Specific targeting of interleukin-23p19 as effective treatment for psoriasis. *J Am Acad Dermatol* 2014, 70(3):555-61.

[9] Trinchieri G. and Gerosa F. Immunoregulation by interleukin-12. *J Leukoc Biol* 1996, 59(4):505-11.

## Clinical rationale

PsA is a multifaceted and heterogeneous disease, which affects the joints, soft tissues (enthesitis and dactylitis) and skin. All of the disease manifestations may affect functional capacity and QOL. There is also increased mortality with persistent, severely active PsA. Peripheral joint involvement with PsA may be polyarticular (35 to 40%) or oligoarticular (20 to 35%) and axial involvement (spondylitis) has been reported in 10 to 25% of patients. The PsA radiographic spectrum is highly variable and includes patients with mild, non-destructive disease to those with severe and debilitating deformities due to progressive joint disease. The diverse radiographic findings seen in PsA include erosions and joint space narrowing (JSN), soft tissue changes and new bone formation.

USK neutralises the bioactivity of IL-12 and IL-23, which are pro-inflammatory cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 stimulates natural killer cells and drives the differentiation of CD4+ T-cells toward the T-helper 1 (Th-1) phenotype and stimulates the production of interferon gamma (IFNγ). IL-23 induces the T-helper 17 (Th17) pathway and promotes the secretion of various other pro-inflammatory cytokines such as IL-17, IL-21 and IL-22. Both IL-12 and IL-23 are highly expressed in the synovium and entheses of patients with PsA and patients with skin psoriasis over-express these cytokines in psoriatic plaques. In addition, mouse models of arthritis demonstrate that the injection of IL-23 has the capacity to provoke and maintain entheseal inflammation. Overall, by binding the shared p40 subunit of IL-12 and IL-23, USK appears to have robust biological plausibility in being able to treat both psoriasis and PsA through interruption of the TH1 and Th17 cytokine pathways, which are central to the pathology of the diseases.[10]

Current approved treatment options in Australia for moderately to severely active PsA include non-steroidal anti-inflammatory drugs (NSAIDs); conventional non-biological DMARDs such as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF) and cyclosporine as well as several anti-tumour necrosis factor drugs (anti-TNF) drugs. Recent literature suggests that conventional DMARDs have modest efficacy in treating the signs and symptoms of PsA. In addition, while anti-TNF drugs have been shown to demonstrate significant efficacy in treating active PsA, a substantial proportion of patients are not achieving meaningful American College of Rheumatology (ACR) responses. Based on the current literature for anti-TNF therapies, ACR20[11] response rates range from 50 to 60% and ACR50 response rates are approximately 30 to 40%. As such, there is an unmet need for additional therapies for active, treatment refractory PsA. USK is a monoclonal antibody therapy that has a different mechanism of action to conventional DMARDs and anti-TNF drugs.

## Guidance

This submission was consistent with the pre-submission planning advice given to the sponsor by the TGA. There is one specific regulatory guideline relevant to the requested indication in PsA. The TGA has adopted the EU guideline *Guideline on Clinical Investigation for Medicinal Products for the Treatment of Psoriatic Arthritis* (effective 5 February 2008).

For the proposed extension of treatment indication to include active PsA, the sponsor has submitted 2 pivotal studies (PSUMMIT I and II), which is supported by a single Phase II trial (C0743T10). Both pivotal studies have provided reports at 24 and 52 weeks for efficacy assessment, and safety evaluations at 16, 24 and 52 weeks of treatment follow-up. One of the pivotal Phase III studies (PSUMMIT I) is ongoing but the long-term data (108

[10] Schett G, Elewaut D, McInnes IB, et al. How Cytokine Networks Fuel Inflammation: Toward a cytokine-based disease taxonomy. Nat Med 2013; 19: 822-824.
[11] ACR score is a scale to measure change in rheumatoid arthritis symptoms. It is named after the American College of Rheumatology. Different degrees of improvement are referred to as ACR20, ACR50, ACR70.

weeks of treatment follow-up) is not yet available for consideration at this stage. PsA is a chronic disease and therefore, symptomatic treatment is expected to be maintained in the long term. The regulatory guideline relating to the assessment of a drug treatment in PsA states that clinical efficacy can be demonstrated over 12 to 24 weeks of therapy in a controlled trial, but maintenance of treatment effect requires longer duration studies (for example, one year). The guideline also recommends for the provision of an adequate safety database that a minimum of 300 to 600 patients should be exposed to the proposed marketing dose for 6 months and at least 100 patients be exposed for a minimum of 12 months.

In PsA subjects, there are 5 main domains to assess efficacy (each with recommended instruments):

1. Improvement of symptoms and signs of peripheral arthritis (for example, using ACR clinical criteria)
2. Improvement of physical function (for example, using Health assessment questionnaire (HAQ))
3. Improvement of symptoms and physical function related to axial disease (for example, using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI))
4. Slowing or prevention of structural damage (for example, using modified Sharp score[12]), and
5. Prevention of disability.

This application in patients suffering PsA includes the additional component of inhibition of structural damage as measured by serial plain X-ray.

In this submission, the sponsor has provided an integrated analysis report of the data collected in the 2 pivotal Phase III studies at 24 and 52 weeks of treatment, which assessed the rate of joint damage progression by plain X-ray. The relevant regulatory guideline regarding PsA states that radiographs should be taken at fixed and pre-defined time points without specifying anything further about these time points. However, for comparative purposes the EU guideline on RA[13] requires evidence of maintenance of radiographically demonstrated benefit out to 2 years, the first year of which must be blinded data acquisition. The PsA regulatory guideline also recommends that assessment of other important complementary domains such as skin disease activity, enthesitis, inflammatory markers (Erythrocyte Sedimentation Rate (ESR) or C-reactive protein (CRP)), quality of life measures and global disease assessments (by patients and/or physicians).

## Contents of the clinical dossier

### *Scope of the clinical dossier*

The submission contained the following clinical information:

- All 3 of the efficacy/safety studies contributed pharmacokinetic and pharmacodynamic data.
- 1 population pharmacokinetic analysis.
- 2 pivotal (Phase III) efficacy/safety studies; PSUMMIT I and PSUMMIT II.
- No dose-finding studies.

[12] The Sharp scoring method was first developed for scoring radiologic abnormalities in the hands and wrists of patients with rheumatoid arthritis.A
[13] CPMP/EWP/556/95 (Rev 1) Points to consider on clinical investigation of medicinal products other than NSAIDs for the treatment of rheumatoid arthritis.

- 1 non-pivotal (Phase II) efficacy/safety study; C0743T10.
- Integrated analysis of radiographic data collected in the 2 pivotal Phase III studies.

***Paediatric data***

The submission did not include paediatric data.

***Good clinical practice***

All of the studies in the USK clinical development program for the treatment and prevention of PsA were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

## Pharmacokinetics

### Studies providing pharmacokinetic data

All 3 of the PsA studies collected data for pharmacokinetic (PK) assessment in the target population.

### Evaluator's conclusions on pharmacokinetics

The sponsor has provided new PK data (trough USK concentrations collected every 1to 4 weeks over 36 to 52 weeks of treatment) in this submission for adult patients with active PsA. The sponsor is proposing minor changes to the PK section of the current PI to include the new PK data.

The key PK findings for use in patients with active PsA are:

- Dose proportionality in serum USK concentration was observed when comparing mean serum USK concentrations between the 45 mg and 90 mg groups.
- There was no evidence of accumulation in serum USK concentrations over time.
- A higher proportion of subjects with below the limit of quantification (BLQ) trough serum USK concentrations were observed in the 45 mg dose group compared with the 90 mg group.
- Within each dose group, subjects weighing >100 kg had lower mean serum USK concentrations compared with subjects weighing ≤ 100 kg. When compared across 45 mg and 90 mg groups, mean serum USK concentrations in subjects >100 kg in the 90 mg group were comparable to those observed in subjects ≤100 kg receiving 45 mg injections. Both Phase III studies and the population PK analysis confirmed this observation. These findings support the proposed dosing of USK 90 mg injections in subjects weighing >100 kg.
- Within each dose group of the PSUMMIT I Study, mean serum USK concentrations in subjects who received MTX concomitantly were moderately higher compared with those in subjects who did not receive MTX but the other 2 studies and the population PK analysis did not support this observation.
- In the PSUMMIT II Study, subjects previously exposed to anti-TNF drugs had generally lower serum USK levels, which have may have been confounded by other variables such as a higher mean body weight and a higher incidence of anti-USK antibodies.

Subjects who developed anti-USK antibodies had significantly lower trough USK concentrations as a result of increased plasma clearance of USK.

## Pharmacodynamics

### Studies providing pharmacodynamic data

In this submission, a limited amount of pharmacodynamic (PD) data was collected in the PSUMMIT I and C0743T10 studies. In particular, the effects of USK on serum biomarkers of interest were assessed in both studies and the PSUMMIT I Study also examined the potential effect of USK on various types of T-lymphocytes.

### Evaluator's conclusions on pharmacodynamics

The serum biomarker data from the PSUMMIT I Study indicates that PsA produces systemic inflammation that is measurable in the serum. However this observation was not supported by the Phase II trial (C0743T10) and no strong associations were observed between any serum biomarkers and baseline disease severity, or joint and/or skin response. A wide range of expression levels were observed for several of the analytes in the PsA population as a whole and this heterogeneity may contribute to the lack of significance of a marker when assessed at the level of the population rather than by individual response. Two analytes showed weak but significant correlation to the severity of joint disease (IL-6 and MCSF-1 correlated with Disease Activity Score (DAS28) response[14]) but there was no correlation seen with any analyte and the severity of skin disease (Psoriasis Area and Severity Index (PASI) 75[15]). Inflammation markers such as vascular endothelial growth factor (VEGF), Macrophage Colony-Stimulating Factor 1 (MCSF-1) and YKL-40[16] showed modest differences in serum concentrations, primarily at Week 4 when USK-treated subjects were compared to placebo-treated subjects. These decreases may be related to the PD effects of USK in subjects with PsA. Furthermore, USK does not appear to have an effect on circulating immune cells (the various types of T- and B-lymphocytes).

## Dosage selection for the pivotal studies

The USK dose examined in both PSUMMIT studies was justified from the results of the 2 pivotal Phase III trials of USK in subjects with psoriasis (Studies CO743T08 and C0743T09) and the Phase II C0743T10 Study in subjects with PsA (as part of this submission).

Studies C0743T08 and C0743T09 evaluated the efficacy and safety of 2 dosing regimens for USK in the treatment of moderate to severe plaque psoriasis: 45 mg at given in Weeks 0 and 4 followed by q12w dosing thereafter, and 90 mg administered at Weeks 0 and 4 and subsequently q12w. Both USK dosing regimens led to a statistically significant, rapid onset of efficacy in adult patients with skin psoriasis. Higher proportions of subjects (66.4% to 75.7% across the USK treatment groups in each study) compared with subjects in the placebo group (3.1% to 3.7%) achieved a PASI 75 response at Week 12 (the primary endpoint of both pivotal trials in psoriasis). Furthermore, with maintenance dosing of q12w in both studies, PASI response rates continued to improve up until Week 28 of follow-up, with consistent treatment related results observed across both studies.

[14] The DAS28 provides you with a number on a scale from 0 to 10 indicating current RA disease activity.
- Remission: DAS28 ≤ 2.6
- Low Disease activity: 2.6 < DAS28 ≤ 3.2
- Moderate Disease Activity: 3.2 < DAS28 ≤ 5.1
- High Disease Activity: DAS28 >5.1

[15] The Psoriasis Area and Severity Index (PASI) is a score used by doctors and nurses to record psoriasis severity. It combines the severity (erythema, induration and desquamation) and percentage of affected area.
[16] YKL-40, also called human cartilage glycoprotein-39 (HC gp-39), is a member of family 18 glycosyl hydrolases. YKL-40 is secreted by chondrocytes, synovial cells, and macrophages.

In contrast to the 2 psoriasis trials, Study C0743T10 did not evaluate a USK maintenance dosing regimen. In this Phase II trial, patients were randomly assigned to 1 of 2 treatment groups. The first group (n=76) received 4 weekly injections of USK 90 mg at Weeks 0, 1, 2 and 3. The second group (n=70) received matching placebo injections at Weeks 0, 1, 2 and 3 and then crossed over to receive USK at Weeks 12 and 16. The primary efficacy endpoint was assessed at 12 weeks but subjects were followed through to 36 weeks post-baseline.

Despite the design, Study C0743T10 appeared to show that USK had a maintenance of effect (as reflected by the rate of ACR20 and ACR50 response and PASI response) for at least 12 weeks following the last dose of USK administered whether it was following the initial 4 weekly doses of USK 90 mg or the 2 doses of USK 90 mg given 4 weeks apart in placebo subjects who crossed over to USK at Week 12. Eventually, however, it did appear that USK had a waning effect within 16 to 20 weeks of last dose administered in a small number of subjects indicating, as with all biologic agents for the treatment of PsA, that maintenance dosing would be indicated. In addition, a greater waning of USK effect was noted in the proportion of PASI 75 responders 12 to 16 weeks after their last dose of USK.

Unlike Studies C0743T08 and C0743T09, the 45 mg dose of USK was not examined in Study C0743T10. During the course of Study C0743T10, Centocor (the drug manufacturer) added a filtration procedure during dose preparation for safety reasons. As a result of the filtration process, the volume of USK after filtration was reduced from 1.0 mL to 0.70 mL (hence, the USK dose was reduced from 90 mg to 63mg per injection). The first 36 patients in the study (17 in the USK arm) were randomised prior to the filtration procedure being implemented and received USK 90 mg x 4 injections (360 mg in total). USK treated subjects randomised after the filtration process was commenced (n=59) received USK 63 mg x 4 injections (252 mg in total) and crossover patients had their Week 12 and 16 doses of USK reduced from 90 mg x 2 to 63 mg x 2 (n=57 at Week 12 and n=55 at Week 16). Despite the small patient numbers, there was little difference in the rate of ACR20 response after 12 weeks of exposure in subjects who received doses of USK between 126 mg (2 x 63 mg doses) and 360 mg (4 x 90 mg doses), and therefore the sponsor concluded that an induction regimen of USK 90 mg to 180 mg (based on 2 doses of 45 mg or 90 mg) seemed reasonable for examination in the Phase III PsA study program.

In summary, the combined results of Studies C0743T08, C0742T09 and C0743T10 suggested that the USK dose regimen of either 45 mg or 90 mg at Weeks 0 and 4, followed by q12w administration of USK thereafter as maintenance therapy was appropriate to further evaluate the induction and maintenance of both skin and joint responses in adult patients with active PsA. Hence, both of these USK dose regimens were investigated in the 2 pivotal Phase III Studies in PsA (PSUMMIT I and II). In addition, the incidence and doses of background treatment with conventional DMARDs (mainly, MTX), CS and NSAID when used by patients in the pivotal studies were appropriate, and consistent with contemporary clinical practice in Australia.

## Efficacy

### Studies providing efficacy data

### Evaluator's conclusions on efficacy

***Indication 1: Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms, including the inhibition of structural damage, of active psoriatic arthritis in adult patients (18 years or older).***

This submission contains 2 pivotal Phase III studies (PSUMMIT I and II) in adult subjects with PsA, and 1 non-pivotal, Phase II trial (Studies C0743T10) to support the extension of

treatment indication. One of the pivotal studies (PSUMMIT I) is ongoing with a planned 108 weeks of treatment follow-up. In this submission, both Phase III studies submitted a 52 week efficacy report. Both Phase III studies recruited adult patients with active disease (well defined) and the diagnosis of PsA was in accordance with best practice (using the CASPAR diagnostic criteria). Both of the Phase III had a 16 week placebo controlled period and the primary efficacy endpoint was assessed at 24 weeks. The supporting Phase II study (C0743T10) assessed the primary efficacy outcome at 12 weeks but continued collecting data up to 36 weeks.

This submission is seeking an indication in active PsA, and in general is consistent with the TGA adopted EU guideline pertaining to the requested extension of indication.[17] In the Phase III trials, the choice of clinical (joints and skin), physical functioning and QOL endpoints as well as the statistical analysis were appropriately performed.

The baseline demographic and disease related characteristics of patients in each of the 3 studies are similar to those in the anticipated Australian patient cohort and therefore generalisation of these results to the Australian context is expected. However, there are some caveats to the generalisability of the treatment population. For example, all of the trials excluded patients who were at a significant risk of infection or who had various abnormal laboratory results at baseline (such as abnormal haematology or liver function tests).

The pivotal trials enrolled patients with moderately-severely active PsA and demonstrated that USK is an effective treatment in those who have either failed to respond to conventional treatment options such as DMARDs (mainly MTX) and/or NSAID. In a significant subset of patients in the PSUMMIT II (as well as Study C0743T10) trial, exposure to one or more anti-TNF drugs was additionally documented.

The primary efficacy endpoint of both Phase III studies was the proportion of subjects who achieved an ACR20 response at 24 weeks (clinical response criteria) and this was achieved in both trials. In the PSUMMIT I Study, more patients treated with USK (42.4% [87/205] treated with 45 mg injections and 49.5% [101/204] receiving 90 mg) achieved this outcome as compared to 22.8% (47/206) of patients in the placebo group. In the PSUMMIT II Study, the ACR20 response rates showed a similar benefit in favour of USK but not at such an overall level of response. This probably reflects the treatment refractory nature of this population compared to the PSUMMIT I study cohort. In the PSUMMIT II Study, more patients treated with USK (43.7% [45/103] treated with 45 mg and 43.8% [46/105] receiving 90 mg) achieved an ACR20 response at 24 weeks compared to those treated with placebo (20.2% (21/104)).

Many secondary efficacy measures examining other clinical outcomes (enthesitis and dactylitis scores) and functional endpoints (HAQ-DI) also demonstrated clinically significant changes with USK. Additionally, improvements in measures of skin disease activity (PASI response) and health related QOL were also attained with USK therapy. USK also showed efficacy in the subgroup of patients with co-existent inflammatory spondylitis but the BASDAI score has not been validated in subjects with PsA. In the 2 pivotal Phase III studies, clinical response was maintained for up to 52 weeks of treatment but observations taken after 24 weeks were not placebo controlled. The supporting Study C0743T10 supported the observation that USK therapy results in clinically meaningful improvements in joint disease activity. Clinical response to USK appears to peak approximately 12 weeks after treatment initiation.

Although the 2 pivotal Phase III studies were not designed to compare the efficacy of concomitant MTX or of anti-TNF experienced versus anti-TNF naïve groups, USK

[17] CPMP/EWP/438/04 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis' (effective 5 February 2008)

demonstrated superior efficacy compared to control therapy regardless of concurrent MTX use and, importantly among the majority of anti-TNF experienced patients, although to a lesser degree than that observed in anti-TNF naïve subjects. For the subset of patients (n=45) in the PSUMMIT II trial who had used 3 or more anti-TNF drugs previously, the rate of ACR20 response at 24 weeks between USK and placebo showed no significant treatment related difference. Consistently, patients in both the PSUMMIT I and II studies weighing >100 kg demonstrated lower overall rates of clinical response (joints and skin) than those weighing ≤ 100 kg. Pharmacokinetic factors (lower mean serum USK concentrations) may contribute to the observation of lower overall clinical response in patients weighing >100 kg. In the PSUMMIT I Study (but not the PSUMMIT II trial), the USK 90 mg dose showed a numerical advantage over the USK 45 mg dose in achieving various levels of ACR response in the subgroup of patients weighing >100 kg. Such an observation supports the proposed dosing regimen of using 90 mg USK injections (versus USK 45 mg therapy) in subjects weighing >100 kg.

To determine the effect of USK on the inhibition of structural progression an integrated analysis of the X-ray data from both Phase III studies was pre-specified. This was a major secondary efficacy endpoint of the clinical study program. The primary X-ray endpoint was the mean change from baseline to week 24 in the total modified van der Heijde-Sharp (vdHS) score[18]. This was achieved using the combined dataset. However, when the individual trials were analysed independently the beneficial radiographic effect of USK was only observed in the PSUMMIT I cohort and no treatment related effect was observed in the PSUMMIT II Study. The sponsor proposes that the results of this trial may have been confounded by the large amount and non-random pattern of missing radiographic data, particularly in the placebo group. In addition, for subjects weighing >100 kg, no treatment effect was seen in subjects receiving USK treatment when compared to placebo treated subjects, though the number of subjects in this subpopulation was smaller and the magnitude of progression of structural damage was low in the placebo group.

Overall, the data in this submission supports the efficacy of USK in the treatment of active PsA from a clinical perspective (in beneficially treating the symptoms and signs as well as improving physical functioning) in those with moderate-severely active disease at baseline with or without concurrent DMARD and/or NSAID. Approximately half of all subjects in the three PsA studies took MTX concurrently with USK and the beneficial clinical responses in those not taking concomitant MTX were similar. Hence the sponsor has justified the claim of using USK in patients with PsA with or without MTX.

However, the current submission does not provide a sufficiently robust dataset for the claimed additional feature of inhibition of structural progression (as measured by X-ray of peripheral joints). Further longitudinal X-ray follow-up to 2 years of the PSUMMIT I population with a pre-defined statistical analysis plan would be required before that additional claim can be made. At this stage, a statistically significant inhibition of structural damage progression after 24 weeks of treatment with USK in subjects with active PsA has only been observed in the anti-TNF naïve cohort of PSUMMIT I and the result has not been replicated in the accompanying PSUMMIT II trial.

## Safety

### Studies providing safety data

- No studies assessed safety as the primary outcome. The following studies provided evaluable safety data:

[18] A composite score (0-448) of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in the hands and feet.

- Pivotal efficacy studies (PSUMMIT I and II)
- Study C0743T10 was a non-pivotal, Phase II trial that provided safety data on general AEs, AEs of special interest (for example, injection site reactions), blood parameters (haematology and clinical chemistry), physical examination and anti-drug antibodies
- The submission also contained summary safety data from clinical studies in the approved indication of psoriasis (a total of 4 studies in which 3117 subjects received at least 1 dose of USK; treatment follow-up for up to 5 years) and 2 Phase II studies in Crohn's disease. The studies were provided for summary comparative purposes and did not reveal any significant differences in the incidence and type of AEs according to underlying treatment indication.

**Patient exposure**

Up to the end of the current reporting period for each of the three PsA studies, a total of 914 subjects have received treatment with USK (Table 2). Of these subjects, 75.7% (692 subjects) have been exposed to USK for at least six months and 23.3% (213 subjects) have been exposed for at least one year. In the combined PsA dataset, more than 300 subjects have been exposed to both proposed doses of USK (45 and 90 mg) for at least 6 months. The median exposed dose in the USK 45 mg group is 135 mg and the median exposed dose in the 90 mg cohort is 270 mg. During the placebo-controlled phases of all 3 PsA trials (up to Week 16 for the PSUMMIT studies and up to Week 12 in Study C0743T10), the average duration of follow-up and treatment exposure were comparable between the placebo and USK treatment groups. After the placebo-controlled periods, the average duration of follow-up and average duration of exposure were lower for subjects in the control groups than for subjects in the USK treatment arms.

In this submission, the sponsor also presented summaries of safety data from other treatment indications (psoriasis and Crohn's disease) in support of the PsA safety data. Some of this data has already been evaluated by the TGA as part of obtaining a treatment indication in psoriasis. There are 4 psoriasis trials, which have followed patients for up to 5 years. In the psoriasis studies, a total of 1168 subjects have been exposed to USK 45 mg and 1438 subjects have received USK 90 mg for at least 6 months (Table 2). In terms of long-term safety, 307 subjects in the 45 mg group and 432 subjects in the 90 mg cohort have received USK for at least 5 years. USK has also been evaluated in 2 Phase II trials in Crohn's disease (C0379T07 and C0743T26). A total of 158 subjects (26.4% of 599) were exposed to USK for at least 6 months with intravenous doses up to 6 mg/kg.

**Table 2: Summary of USK Exposure in Psoriatic Arthritis Studies and Other Indications**

| | PsA Studies[b] | | | Psoriasis Studies[c] | | | Crohn's Disease Studies[d] |
|---|---|---|---|---|---|---|---|
| | 45 mg | 90 mg | Combined | 45 mg | 90 mg | Combined | Combined Ustekinumab |
| Subjects treated with ustekinumab[a] | 473 | 497 | 914 | 1319 | 2001 | 3117 | 599 |
| Duration of ustekinumab exposure | | | | | | | |
| At least 6 months[e] | 345 (72.9%) | 309 (62.2%) | 692 (75.7%) | 1168 (88.6%) | 1438 (71.9%) | 2414 (77.4%) | 158 (26.4%) |
| At least 1 year[f] | 88 (18.6%) | 108 (21.7%) | 213 (23.3%) | 901 (68.3%) | 1136 (56.8%) | 1855 (59.5%) | 0 |
| At least 18 months[g] | 0 | 0 | 0 | 808 (61.3%) | 1025 (51.2%) | 1697 (54.4%) | 0 |
| At least 2 years[h] | 0 | 0 | 0 | 713 (54.1%) | 986 (49.3%) | 1653 (53.0%) | 0 |
| At least 3 years[h] | 0 | 0 | 0 | 617 (46.8%) | 886 (44.3%) | 1569 (50.3%) | 0 |
| At least 4 years[h] | 0 | 0 | 0 | 566 (42.9%) | 746 (37.3%) | 1482 (47.5%) | 0 |
| At least 5 years[h] | 0 | 0 | 0 | 307 (23.3%) | 432 (21.6%) | 838 (26.9%) | 0 |
| Avg number of ustekinumab administrations | 3.2 | 3.3 | 3.4 | 13.6 | 12.4 | 13.7 | 2.0 |
| Total dose (mg) | | | | | | | |
| N | 473 | 497 | 914 | 1319 | 2001 | 3117 | 599 |
| Mean (SD) | 143.1 (48.39) | 274.3 (113.51) | 223.2 (107.30) | 611.0 (430.93) | 1116.7 (921.81) | 975.4 (845.62) | 331.8 (163.20) |
| Median | 135.0 | 270.0 | 225.0 | 540.0 | 810.0 | 810.0 | 360.0 |
| IQ range | (90.0; 180.0) | (252.0; 360.0) | (135.0; 270.0) | (180.0; 990.0) | (180.0; 1980.0) | (180.0; 1800.0) | (236.7; 379.8) |
| Range | (45; 270) | (63; 450) | (45; 450) | (45; 1395) | (45; 2880) | (45; 2880) | (42; 1035) |

[a] PsA studies include C0743T10, CNTO1275PSA3001, and CNTO1275PSA3002. Psoriasis studies include C0379T04, C0743T08, C0743T09, and C0743T12. Crohn's disease studies include C0379T07 and C0743T26.
[b] Placebo crossover subjects were included in the ustekinumab columns after crossover to ustekinumab. For C0743T10, subjects who were randomized to ustekinumab were included in 90 mg column. For CNTO1275PsA3001 and CNTO1275PsA3002, subjects who were dose escalated from 45 mg to 90 mg were switched to the 90 mg column following dose escalation.
[c] Placebo crossover subjects and etanercept crossover subjects were included in the ustekinumab columns after crossover to ustekinumab. For C0743T09, subjects who were dose escalated from 45 mg to 90 mg were switched to the corresponding column following dose escalation.
[d] Placebo crossover subjects were included in the ustekinumab column after crossover to ustekinumab
[e] The duration between the first and last ustekinumab administration was at least 14 weeks.
[f] The duration between the first and last ustekinumab administration was at least 38 weeks.
[g] The duration between the first and last ustekinumab administration was at least 62 weeks.
[h] At least 2 years: The duration between the first and last ustekinumab administration was at least 88 weeks. At least 3 years: The duration between the first and last ustekinumab administration was at least 140 weeks. At least 4 years: The duration between the first and last ustekinumab administration was at least 192 weeks. At least 5 years: The duration between the first and last ustekinumab administration was at least 240 weeks.

## Safety issues with the potential for major regulatory impact

### *Risk of infection, including opportunistic infection*

USK has been identified to be associated with a potential increased risk of infection, including reactivation of latent tuberculosis. Screening for tuberculosis was an entry requirement of both pivotal studies in this submission. No patient in the 3 PsA trials developed reactivation of latent tuberculosis. Herpetic infections were reported at a very low frequency in both pivotal studies, with no treatment related association being apparent. The overall rate of infection related serious adverse events (SAEs) was similar in USK treated subjects versus placebo patients in both pivotal studies but between Weeks 24 and 52 to 60, several cases of serious infection were observed in both Phase III studies.

### *Malignancies, including skin cancer*

In the placebo controlled periods of the PsA trials, the incidence of malignancies (excluding non-melanoma skin cancer) was 0.16 per 100 Patient-Years (PY) of follow-up for those who received USK (1 subject in 615 PY of follow-up) compared with 0.35 per 100 PY of follow-up in the placebo cohort (1 subject in 287 PY of follow-up). The incidence of non-melanoma skin cancer was 0.65 per 100 PY of follow-up for those who received USK (4 subjects in 615 PY of follow-up) compared with 0.70 per 100 PY of follow-up in the placebo group (2 subjects in 287 PY of follow-up). The short-term data for the risk of malignancy in patients with PsA treated with USK appears relatively benign and within expectations, however, the clinical studies thus far reported have insufficient treatment follow-up periods (ranging from 36 to 60 weeks) in this submission to assess the malignancy potential of USK in the target populations of PsA. Updated data from the psoriasis population experience, which is significantly larger, does not indicate an increased overall risk of malignancy (excluding non-melanoma skin cancer) when using USK, however, this issue will require ongoing surveillance in the target populations if approval is granted.

### *Injection site and hypersensitivity reactions*

ISRs are uncommon, mild in severity and have not been associated with premature discontinuation of study medication. Furthermore, no major hypersensitivity reactions have been observed.

### *Cardiovascular safety*

Patients with PsA are known to be at an increased risk of occlusive atherosclerotic vascular disease such as myocardial infarction and stroke. A total of 4 major adverse cardiovascular events have been recorded in the PsA trials included in this submission. None of the 4 events resulted in death; 2 of the cases were myocardial infarction (1 in a placebo treated subject and the other in a patient given USK 45 mg injections) and the other 2 reports related to stroke (USK 45 mg and USK 90 mg). The rate of major cardiovascular adverse event is low (0.55-0.78 per 100 PY) and within expectations for the target population.

### *Unwanted immunological events*

The rate and consequences of developing anti-USK antibodies has already been discussed above. The formation of anti-drug antibodies (ADAs) does not appear to be associated with experiencing adverse events (AEs) but results in increased plasma clearance of the drug, which potentially may affect efficacy.

In this submission, no subjects developed clinical consequences consistent with systemic autoimmune disease (such as systemic lupus erythematosus) or major neurologic disorders. However, 1 subject (in the placebo to USK 45 mg crossover group) in Study C0743T10 developed rebound of psoriasis within 3 months of receiving their last dose of USK.

### *Other safety issues*

*Safety in special populations*

In the PsA studies to date, 3 subject pregnancies and 2 partner pregnancies have been reported. No further information on the outcome of each of these pregnancies has been provided.

No formal study of drug-drug interaction has been performed with USK and there is no data on the effect of USK upon vaccine responses in the PsA population.

During the three PsA studies, there was no safety signal to indicate that the concomitant use of MTX or past exposure to anti-TNF therapy was associated with an increased incidence or type of AE. However, obesity (subject weight >100 kg) does appear to confer an increased risk of AEs, particularly for infection related AEs. This observation is not unexpected as it has been observed for various drugs including MTX and other biologic DMARDs.

## Postmarketing data

USK first received marketing approval for the treatment of psoriasis in December 2008 and is currently approved in over 65 countries for this indication. At the time of submission in Australia (December 2013), no postmarketing reports anywhere in the world for the treatment indication of PsA were available as this indication was only approved in Europe and USA in September 2013. As of June 30, 2012 7 Periodic Safety Update Reports (PSURs) have been submitted. Hypersensitivity reactions (including rash and urticaria post-injection) and serious allergic reactions (including anaphylaxis and angioedema) have been identified from spontaneous adverse drug reaction (ADR) reports. The other safety concerns under surveillance are serious infection (including tuberculosis and salmonella), malignancies, major adverse cardiovascular events, neurologic disorders

(including facial palsy) and pregnancy outcomes. There is also concern in the dermatology literature of a possible association between USK use in adult patients with psoriasis and the development of non-melanoma skin cancers, particularly in those >60 years of age with a prior history of prolonged immunosuppressant treatment or psoralen plus ultraviolet A therapy. This potential safety concern remains under surveillance.

**Evaluator's conclusions on safety**

In this submission, the total clinical safety dataset for the use of USK in adult patients with active PsA consists of 914 patients involved in two pivotal Phase III studies (PSUMMIT I and II) and 1 supporting Phase II trial (C0743T10), 692 (75.7%) of whom received USK for at least 6 months and 213 (23.3%) subjects were exposed to USK for at least one year. USK therapy was given by SC injection either at a dose of 45 mg, 63 mg or 90 mg. Both of the proposed doses in PsA (45 mg and 90 mg) had more than 300 subjects exposed to USK for at least 6 months. Approximately half of the patients in the dataset received concurrent MTX, more than 75% were taking concomitant NSAID and approximately one sixth were taking concurrent low dose oral corticosteroids (CS). In the PSUMMIT II trial, more than half of all subjects had received prior biologic therapy, mainly with anti-TNF therapy. Overall, there is a sufficient volume of data to make a meaningful assessment of USK safety for up to 52 weeks of treatment in the newly proposed treatment indication of active PsA.

Infection was the most common adverse event (AE) recognised in the PsA studies and these appeared to occur at a slightly higher frequency in the USK treatment groups versus control during the placebo controlled treatment periods (12 to 16 weeks). The majority of infections were mild in severity, self-limiting and were predominately either nasopharyngitis or upper respiratory tract infections (URTI). Some gastrointestinal AEs were also more common in USK treated subjects, particularly diarrhoea and nausea. The use of concurrent MTX or prior exposure to anti-TNF therapies did not appear to increase the overall risk of AEs, including infection related AEs. However, subject weighing >100 kg had a higher incidence of overall and infection related AEs. SAEs including serious infection related events were reported in a low proportion of USK treated patients in both pivotal trials (<3%). No patients developed reactivation of latent tuberculosis and no other significant opportunistic infections were observed.

Injection site reactions were an uncommon type of AE reported in patients receiving USK (incidence of 1.5 to 2.5% in the Phase III studies). The majority of injection site reactions were mild, resolved without specific intervention and did not result in discontinuation from USK therapy. No acute systemic hypersensitivity reactions were reported with USK in the three PsA trials and only one case of rebound psoriasis was reported in a USK treated subject in the two pivotal studies. Discontinuations due to AEs occurred at a low and similar frequency in USK versus placebo treated subjects.

No deaths were reported in the three PsA studies. Regarding major adverse cardiovascular events, a total of 8 events were recorded in USK treated subjects in the extended follow-up periods (ranging from 36 to 60 weeks) of the three PsA studies. These AEs included five myocardial infarcts, two cases of cerebrovascular accident (including one case of cerebral haemorrhage) and there was one report of atrial fibrillation. All of the patients had significant risk factor profiles for suffering major adverse cardiovascular events and the relationship between these types of AEs and USK remains unclear. Three patients developed malignancies in the PsA studies (two reports in PSUMMIT II and one case in Study C0743T10). Two of the cases related to non-melanoma skin cancer and the other patient suffered breast cancer. Overall, longer periods of treatment follow-up are required to inform about this potential safety signal.

No significant abnormalities of laboratory values (such as elevations in hepatic transaminases) compared with placebo have been associated with USK in the PsA study

program. Some patients developed increases in non-fasting blood glucose and liver function tests which were mild and without associated clinical sequelae. There were couple of cases of significant thrombocytopenia observed in patients treated with USK and mild-moderate asymptomatic lymphopenia has also been observed.

The incidence of PsA subjects developing anti-USK antibodies is approximately 7.1 to 9.3% at 52 to 60 weeks using the combined USK treated datasets in the PSUMMIT studies and their clinical relevance for safety outcomes is yet to be defined with no discernible link to the risk of infection, or injection related reactions. However, the development of anti-USK antibodies may be associated with a lack or loss of efficacy.

In summary, the safety data indicates that USK has an acceptable overall safety profile up to 52 weeks of therapy in the treatment of adult patients with moderately to severely active PsA. There is limited long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and adverse cardiovascular events which will require longitudinal safety follow-up. There are some significant identified safety concerns including the risk of serious infection, opportunistic infection, injection related hypersensitivity and allergic reactions, and neurologic disorders. These safety concerns are consistent with the known profile of USK in the approved indication of psoriasis. Significant pharmacovigilance would be required if approval is granted for extension of treatment indications. This would include vigilance for opportunistic infections, adverse cardiovascular events and malignancy (particularly, non-melanoma skin cancers).

## First round benefit-risk assessment

### First round assessment of benefits

The benefits of USK in the proposed usage are:

- Clinically meaningful improvements in the clinical signs and symptoms of PsA (ACR response criteria), as well as physical functioning and QOL indices when given to patients with active PsA who have failed to respond to conventional treatment (DMARD [mainly MTX] and NSAID).
- In addition to the joint disease of PsA, USK is an effective therapy for associated soft tissue manifestations such as enthesitis and dactylitis as well as co-morbidities such as skin psoriasis and spinal disease symptoms.
- Provides an alternative biologic therapy (different mechanism of action) to anti-TNF drugs in patients with active PsA who have failed to respond to conventional treatment.
- Convenient dosing schedule (every 12 weeks in the maintenance phase of therapy) using a convenient mode of administration (SC injection via prefilled syringe).

### First round assessment of risks

The risks of USK in the proposed usage are:

- Increased incidence of minor infection (particularly nasopharyngitis and URTI) compared with placebo as well as other mild AEs such as diarrhoea, nausea and headache.
- Potential for serious infection including reactivation of latent tuberculosis and other serious opportunistic infections.
- Local injection site reactions which are generally mild and transient and do not result in permanent discontinuation from USK.

- Potential increased risk of malignancy (particularly, non-melanoma skin cancers) and adverse cardiovascular events requiring long-term surveillance.
- Formation of anti-USK antibodies which results in increased plasma clearance of USK and possible loss or lack of efficacy.
- Slower onset of action than anti-TNF drugs in treating the symptoms and signs of active PsA but similar response rates at 52 weeks of treatment follow-up (indirect data comparison).
- Patients weighing >100 kg require a larger dose (90 mg) compared to those weighing ≤100 kg (45 mg).

### First round assessment of benefit-risk balance

The benefit-risk balance of USK for up to 60 weeks of treatment follow-up in the target population of adult subjects with active PsA is favourable.

## First round recommendation regarding authorisation

The clinical evaluator recommends acceptance of the sponsor's proposed extension of treatment indications for USK to include the treatment of active PsA. Approximately half of all subjects in the three PsA studies took MTX concurrently with USK and the beneficial clinical responses in those not taking concomitant MTX were similar. Hence the sponsor has justified the claim of using USK in patients with PsA with or without MTX. Furthermore, the studies recruited subjects with active PsA who had failed to adequately respond to conventional treatment (DMARD [mainly MTX] and/or NSAID) but did include a subset of patients with prior biologic therapy exposure (mainly, anti-TNF medicines).

The evaluator recommends the Australia proposed treatment indication include a short phrase consistent with the EU wording indicating that USK be used as a second line therapy following the failure of conventional DMARD and/or NSAID.

The proposed wording of treatment extension in patients with PsA has an additional element relating to inhibition of structural progression of peripheral joint damage by X-ray. The current submission provides robust evidence of improving the symptoms and signs of active PsA as well as physical functioning. However, the radiographic claim has not been sufficiently proven at this stage and requires further evidence of justification before registration is approved. In particular, the current X-ray data is limited to 52 weeks of assessment which is an insufficient time frame to evaluate such a claim. Furthermore, the current X-ray data only shows a positive effect with USK in one of the two pivotal studies (PSUMMIT II did not show a treatment related effect with USK versus placebo at 24 weeks) and in subjects without prior anti-TNF exposure. This observation may have occurred because of the data handling rules and associated imputation factors but nonetheless no consistent treatment related radiographic effect with USK could be demonstrated in the current dataset. It would be important to review the 2 year radiographic data from the PSUMMIT I Study to determine if a robust treatment effect with USK could be observed.

Consistent with the submitted data as well as the approved EU treatment indication wording, the evaluator recommends the following indication wording

> *Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients when the response to previous non-biological DMARD therapy has been inadequate.*

Should approval of the sponsor's proposed extension of indication be granted, the evaluator also recommends that approval of the sponsor's proposed extension of indication be subject to:

- Satisfactory response to the *Clinical questions* (below)
- Regular periodic safety update reports, and
- When available, the sponsor provides the TGA with the final clinical study report for the PSUMMIT I Study (at 108 weeks of treatment follow-up).

## Clinical questions

### Pharmacokinetics

No formal drug-drug interaction studies with Stelara have been performed. Cytokines have the potential to alter the expression of cytochrome P450 (CYP450) enzymes. Could the sponsor comment on whether Stelara has the potential for drug-drug interactions on the basis of an alteration in cytokine levels and/or activity?

## Pharmacodynamics

Has the sponsor evaluated the potential for polymorphisms in the IL-23/Th-17 and IL-12/Th-1 pathways as having an impact upon the effect of Stelara?

## Efficacy

In the current approved product information, dose adjustment (reducing the dose interval from 12 to 8 weeks) is possible for patients with psoriasis demonstrating inadequate response. Could the sponsor confirm that no such dose adjustment strategy is being requested for the psoriatic arthritis treatment indication?

The claim of radiographic benefit with Stelara in patients with active psoriatic arthritis is primarily based on a treatment related effect observed in the PSUMMIT I Study (but not demonstrated in the PSUMMIT II trial) on assessments performed after 24 weeks of treatment. Moreover, for subjects weighing >100 kg, no treatment effect was seen in patients receiving Stelara when compared to placebo treated subjects. Could the sponsor comment on the robustness of the claim of inhibiting structural progression given the limitations of the current dataset (that is, treatment effect has not been consistently demonstrated in both pivotal studies and across all patient subgroups)?

Another limitation of the current X-ray dataset is the duration of treatment follow-up. Although there is no specific regulatory advice on the minimum required time intervals for evaluating X-ray outcomes in psoriatic arthritis, regulatory guidelines in RA recommend a longer period of follow-up (beyond 12 months) before a radiographic claim can be made. Could the sponsor comment on whether the two year radiographic data from the PSUMMIT I Study should be considered before a robust treatment effect with Stelara on radiographic outcomes be assessed?

## Safety

Has the sponsor performed any vaccine sub-studies in patients with psoriatic arthritis to determine the effect of Stelara on protective immune status?

### Second round evaluation of clinical data submitted in response to questions

The sponsor has responded to 6 clinical questions that were raised in the first round clinical assessment (response letter dated 25 August 2014). Each of these responses will be assessed in order.

*Question 1. No formal drug-drug interaction studies with Stelara have been performed. Cytokines have the potential to alter the expression of cytochrome P450 enzymes. Could the sponsor comment on whether Stelara has the potential for drug-drug interactions on the basis of an alteration in cytokine levels and/or activity?*

Although no formal drug interaction studies have been performed, the sponsor reports that it has conducted in vitro studies that indicate that IL-12 and IL-23 do not modulate the expression of the major CYP enzymes, indicating that no dose adjustments are required in patients receiving concomitant CYP450 metabolised drugs with USK. In addition, the US FDA agreed that in vivo drug interaction studies for USK were not required. The sponsor response is acceptable with no further action.

*Question 2. Has the sponsor evaluated the potential for polymorphisms in the IL-23/Th-17 and IL-12/Th-1 pathways as having an impact upon the effect of Stelara?*

The sponsor states that no single nucleotide polymorphisms in the T-helper cell pathway (Th-1 or Th-17) relating to the effect of USK have been identified using immunochip analysis of the PsA data. Hence, it is unlikely that polymorphisms in these immune pathways may influence the effect of USK, which is an acceptable assumption.

*Question 3. In the current approved product information, dose adjustment (i.e. reducing the dose interval from 12 to 8 weeks) is possible for patients with psoriasis demonstrating inadequate response. Could the sponsor confirm that no such dose adjustment strategy is being requested for the psoriatic arthritis treatment indication?*

The sponsor confirms that no dose adjustment for inadequate responders was studied in the PsA clinical studies and therefore a dose adjustment strategy is not being requested for the PsA treatment indication. The dosing discrepancy between the two treatment indications (psoriasis and PsA) has the potential to result in off label use for Stelara in the PsA indication although the proposed PI is clear about the differences in dosing across the two treatment indications.

*Question 4. The claim of radiographic benefit with Stelara in patients with active psoriatic arthritis is primarily based on a treatment related effect observed in the PSUMMIT I Study (but not demonstrated in the PSUMMIT II trial) on assessments performed after 24 weeks of treatment. Moreover, for subjects weighing >100 kg, no treatment effect was seen in patients receiving Stelara when compared to placebo treated subjects. Could the sponsor comment on the robustness of the claim of inhibiting structural progression given the limitations of the current dataset (that is, treatment effect has not been consistently demonstrated in both pivotal studies and across all patient subgroups)?*

The sponsor concurs with the above statement that the beneficial effect of USK on limiting structural damage progression was only observed in the PSUMMIT I Study and for those subjects weighing $\leq$100 kg. As per the original submission, the sponsor provides several possible explanations for the inconsistency of the X-ray results between the PSUMMIT I and PSUMMIT II studies including a higher rate and non-random pattern of missing data observed in the PSUMMIT II Study (versus PSUMMIT I), a smaller heterogeneous population of anti-TNF experienced and naïve patients in the PSUMMIT II Study (versus subjects being TNF naïve in PSUMMIT I) as well as the anti-TNF naïve subpopulation (42% of all subjects) in the PSUMMIT II Study showing lower inflammatory disease activity at baseline (versus PSUMMIT I). All three of the above hypotheses are valid explanations for the inconsistent X-Ray results across the two pivotal PsA trials. In their response, the sponsor has included a post hoc analysis from the anti-TNF naïve subgroup of the

PSUMMIT II Study showing that that those with a higher inflammatory activity at baseline (defined as CRP ≥10 mg/L) had less X-ray progression at 24 weeks (defined as change from baseline in the total modified vdH-S score) when treated with USK (n=39 for the combined USK group) versus control therapy (n=14 subjects), particularly at the 90 mg dose (n=20 subjects). Published literature supports the proposal that elevated CRP values are a risk factor for X-ray progression in PsA.[19] However, a significant limitation of the post hoc, subgroup analyses was that only small patient groups were available to be investigated which makes the results susceptible to invalidity. In addition, in the anti-TNF naïve subgroup of the PSUMMIT II Study with CRP <10 mg/L at baseline, no treatment effect with USK (n=51 for the combined USK group) versus placebo (n=28) was observed. Furthermore, in the anti-TNF experienced subjects of the PSUMMIT II Study, no treatment effect with USK (n=118 for the combined USK group) over control (n=62) was observed, regardless of baseline CRP reading.

In support of the consistency of the findings, the sponsor has also submitted two additional post hoc analyses based on modelling of the X-ray progression using the results of the two anti-TNF naïve populations from the PSUMMIT studies. In these analyses, a logistic regression model based on the PSUMMIT I Study X-ray data was developed using observed data, which was then applied to the anti-TNF naïve subgroup of the PSUMMIT II trial to calculate the predicted progression status. The model showed that the anti-TNF naïve subgroup of the PSUMMIT II Study recorded observed X-ray data (for the change from baseline to week 24 in total modified vdH-S score) within the predicted cut-offs for progression (tested by a 1-sample t-test), suggesting this patient subgroup was similar between the two pivotal trials.

Regarding inhibition of structural damage in subjects weighing >100 kg, the sponsor has included post hoc analyses examining X-ray progression by subject weight (≤100 kg versus >100 kg) within each of the PSUMMIT studies. In the PSUMMIT 1 Study, a treatment effect with USK was observed in both weight strata, though the treatment effect was greater in subjects weighing ≤100 kg but the difference in treatment effect in this subgroup was primarily driven by a larger placebo progression for subjects weighing ≤100 kg (mean change of 1.44 [n=154] in the placebo group versus 0.21 in the combined USK group [n=307]). In the PUSUMMIT I Study, the mean change from baseline to Week 24 in the modified vdH-S score was 0.50 in the placebo treated patients weighing >100 kg (n=52) versus 0.26 in the combined USK treatment group weighing >100 kg (n=102). In the PSUMMIT 2 Study, inhibition of radiographic progression was observed in USK treated subjects weighing ≤100 kg (mean change from baseline of 0.48 [n=147] versus 0.73 in the matched placebo treated cohort [n=74]) mg group, though the magnitude of USK treatment effect was lower than that observed in the PSUMMIT 1 Study. However, in the PSUMMIT II Study, no USK treatment effect was observed in subjects weighing >100 kg (mean change from baseline of 1.37 in the combined USK group [n=60] versus -0.02 in the matched placebo treated group [n=30]).

In summary, the totality of the X-ray data does not demonstrate a consistent robust effect with USK that supports the claim of inhibiting structural progression. The current dataset has not shown a consistent treatment effect with USK in both pivotal PsA studies and across all patient subgroups.

*Question 5. Another limitation of the current X-ray dataset is the duration of treatment follow-up. Although there is no specific regulatory advice on the minimum required time intervals for evaluating X-ray outcomes in psoriatic arthritis, regulatory guidelines in RA recommend a longer period of follow-up (beyond 12 months) before a radiographic claim can be made. Could the sponsor comment on whether the 2 year radiographic data from the*

[19] Gladman DD, Mease PJ, Choy EH, et al. Risk Factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. *Arthritis Res Ther* 2010; 12: R113.

*PSUMMIT I Study should be considered before a robust treatment effect with Stelara on radiographic outcomes be assessed?*

The sponsor provided the Week 100 radiographic results for the PSUMMIT I Study with their response to support the claim of X-ray benefit with USK in PsA. The Week 100 data appropriately focussed on the maintenance of radiographic benefit by evaluating whether the mean changes in the modified total vdH-S score from baseline remained constant or increased over time. The data beyond the 24 week placebo-controlled period is limited by the lack of a control arm as many patients initially randomised to placebo were switched to USK at or before 24 weeks of follow-up.

Between Weeks 52 and 100, subjects who were initially randomised to USK 45 mg (n=205) had a mean change in total modified vdH-S scores of 0.48 (compared with the mean change from baseline to Week 52 of 0.48) and for the USK 90 mg group (n=204) the mean change between Week 52 and 100 was 0.63 (compared to 0.55 for baseline to Week 52). This data indicates that mean changes for both USK treatment groups between the two follow-up periods was similar which is consistent with maintenance of treatment effect. Patients initially randomised to placebo that began receiving USK 45 mg injections at either Week 16 or 24 (n=185 subjects) had a mean change in the total modified vdH-S score of 0.77 between Weeks 52 and 100 compared with a mean change of 1.49 between baseline and Week 52. These results indicate that the rate of radiographic progression between Weeks 52 and 100 decreased with the commencement of USK in those originally administered placebo in the PSUMMIT I Study.

The sponsor's response also included data showing the cumulative change in the modified vdH-S score from baseline to Week 52, as well as the change from baseline to Week 100 (see Table 3). Across all 3 treatment cohorts, the median change from baseline to Week 100 in the total modified vdH-S score was 0. However, the cumulative mean changes from baseline through to Week 100 in all 3 treatment groups increased to suggest accrued X-ray damage over time, albeit at a slower rate in those treated with either dose of USK.

**Table 3: Cumulative Change from Baseline to Week 52 and 100 in total Modified van der Heijde Score in PSUMMIT I Study**

| | | Ustekinumab | | |
|---|---|---|---|---|
| | Placebo → 45 mg [a] | 45 mg | 90 mg | Combined |
| Subjects randomized | 189 | 205 | 204 | 409 |
| Week 52 | | | | |
| Change from baseline | | | | |
| N | 189 | 205 | 204 | 409 |
| Mean (SD) | 1.49 (8.182) | 0.48 (2.471) | 0.55 (2.965) | 0.51 (2.726) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| IQ range | (0.00; 1.00) | (0.00; 1.00) | (0.00; 1.00) | (0.00; 1.00) |
| Range | (-4.5; 104.5) | (-10.5; 12.4) | (-15.5; 17.5) | (-15.5; 17.5) |
| Week 100 | | | | |
| Change from baseline | | | | |
| N | 189 | 205 | 204 | 409 |
| Mean (SD) | 2.26 (12.578) | 0.95 (3.816) | 1.18 (5.052) | 1.07 (4.471) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| IQ range | (0.00; 1.00) | (0.00; 1.00) | (0.00; 1.00) | (0.00; 1.00) |
| Range | (-4.2; 161.0) | (-11.0; 31.0) | (-18.0; 41.0) | (-18.0; 41.0) |

[a] Subjects who did not receive ustekinumab are excluded.

*Question 6. Has the sponsor performed any vaccine sub-studies in patients with psoriatic arthritis to determine the effect of Stelara on protective immune status?*

The sponsor has not performed any vaccine sub-studies in patients with PsA, however, immune responses (antibody titres) to vaccination with tetanus and pneumococcus during the long-term extension of a Phase III study (C0743T09) in psoriasis showed similar responses among USK and control treated subjects. It is reasonable for the sponsor to conclude that patients with PsA are anticipated to demonstrate a similar vaccination

response to those with psoriasis when treated with USK and therefore no specific safety concerns related to this issue are expected.

## Second round benefit-risk assessment

### Second round assessment of benefits

After consideration of the sponsor's responses to the clinical questions regarding efficacy, the benefits of USK in the proposed usage are unchanged from those identified in the First round evaluation.

### Second round assessment of risks

After consideration of the sponsor's responses, the risks of USK in the proposed usage are unchanged from those identified in the First round evaluation.

### Second round assessment of benefit-risk balance

Overall, the benefit-risk balance of USK in the treatment of adult subjects with active PsA is favourable when introduced after a failure to or intolerance of conventional DMARD and/or NSAID therapy.

## Second round recommendation regarding authorisation

The evaluator recommends acceptance of the sponsor's proposed extension of registration for USK to include the treatment indication of active PsA.

However, the clinical evaluator does not recommend acceptance of two additional elements to the sponsor proposed indication wording.

Firstly, the clinical evaluator recommends that the Australia proposed treatment indication include a specific phrase consistent with the EU wording indicating that USK be used as a second line therapy following the failure of conventional DMARD and/or NSAID. The sponsor disagrees with this proposal. However, the pivotal PSUMMIT studies predominately recruited subjects with active PsA who had failed to adequately respond to conventional treatment (DMARD [mainly MTX] and/or NSAID). Approximately 80% of all subjects in the PSUMMIT I Study and about 86% of patients in the PSUMMIT II trial had been previously exposed to DMARDs. In addition, almost 90% of subjects in the PSUMMIT I Study had a past history of taking NSAIDs and approximately 85% of patients in the PSUMMIT II trial had this same history of prior medication use. Overall, the subgroup of enrolled patients in the pivotal Phase PsA trials without previous exposure to DMARDs and/or NSAIDs is too small to make a robust claim of USK being used as a first line therapy in active PsA.

Secondly, the totality of the current X-ray dataset does not robustly support the sponsor claim of inhibition of structural progression as assessed by peripheral joint damage on plain X-ray. In particular, a beneficial radiographic effect with USK has not been consistently demonstrated in both pivotal studies and across all patient subgroups (no significant treatment effect in those previous TNF exposure and/or weighing >100 kg, particularly if CRP values are <10 mg/L).

# V. Pharmacovigilance findings

## Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 11.0 (dated 24 September 2013) with an Australian Specific Annex (ASA) Version 2.1 (dated 18 December 2013) which was reviewed by the TGA's Post-Market Surveillance Branch (PMSB).

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

**Table 4: Summary of ongoing safety concerns**

| | |
|---|---|
| Important identified risks | Serious systemic hypersensitivity reactions<br>Facial palsy<br>Pustular psoriasis |
| Important potential risks | Serious infections including mycobacterial and salmonella infections<br>Malignancy<br>Cardiovascular events<br>Serious depression including suicidality<br>RPLS<br>Exposure during pregnancy<br>Erythrodermic psoriasis |
| Missing information | Use in paediatric patients<br>Use in patients with hepatic impairment<br>Use in patients with renal impairment<br>Use in patients with a history of latent TB or TB<br>Use in patients with concurrent malignancy or a history of malignancy<br>Use after recent vaccination with live bacterial or live viral vaccines<br>Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C)<br>Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy<br>Use in patients with other forms of psoriasis<br>Use in patients who have undergone allergy immunotherapy |

### Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns. This includes follow-up through the use of a questionnaire for all the specified important identified and potential risks, except for the important potential risks 'Serious depression, including suicidality', 'RPLS[20]' and 'Exposure during pregnancy'. Additional pharmacovigilance activities are also being conducted to further monitor all the specified ongoing safety concerns, except the important missing information 'Use after recent vaccination with live bacterial or live viral vaccines' and 'Use in patients who have undergone allergy immunotherapy'.

### Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities are sufficient for the specified ongoing safety concerns, although no risk minimisation activities are proposed for the important potential risks 'Cardiovascular events',' RPLS' and 'Erythrodermic psoriasis' and the important missing information 'Use in patients with other forms of PSO'. Furthermore additional risk minimisation activities are required for the important identified risk: 'Serious systemic hypersensitivity reactions' and the important potential

[20] Reversible posterior leukoencephalopathy syndrome.

risks 'Serious infections including mycobacterial and salmonella infections' and 'Malignancy'.

### Reconciliation of issues outlined in the RMP report

Table 5 summarises the PMSB evaluator's first round evaluation of the RMP, the sponsor's responses to issues raised by the PMSB and the PMSB's evaluation of the sponsor's responses.

**Table 5: Reconciliation of issues outlined in the RMP report**

| Recommendation in RMP evaluation report | Sponsor's response | PMSB evaluator's comment |
|---|---|---|
| 1. The sponsor has advised that the data set package for Australia is the same as submitted in the EU, apart from minor differences due to local regulatory agency administrative requirements. In addition the EU submission was subsequently supplemented with 108 Week data which has not been provided with the Australian package. Nevertheless it is drawn to the Delegate's attention that the approved indications in the EU position Stelara as a second line therapy for the treatment of active psoriatic arthritis in adults rather than as first line therapy as sought for in Australia. The sponsor should explain the reasons for this difference in indications between the EU and Australia in a revised ASA. | The sponsor has provided justification for these differences maintaining that ustekinumab was shown to be effective in both subjects who were exposed to previous DMARD therapy and those who were not exposed to previous DMARD therapy in the Phase III clinical studies. However, such information was not included in the updated ASA. | This evaluator will be guided by the clinical evaluator and Delegate's assessment of the acceptability of the sponsor's justification. Nevertheless it is reiterated that the sponsor should identify and explain the reasons for the difference in indications between the EU and Australia in a revised ASA before this application is approved. |
| 2. Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure | The sponsor states: *'The nonclinical and clinical evaluators have not raised any additional safety considerations* | This is acceptable. |

| Recommendation in RMP evaluation report | Sponsor's response | PMSB evaluator's comment |
|---|---|---|
| that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP. | *that would necessitate additional information within the RMP.'* | |
| 3. The sponsor should provide an explanation for removal of the Phase II trial in sarcoidosis (1275148SCD2001) and the Phase II trial in primary biliary cirrhosis (CNTO1275PBC) from the pharmacovigilance plan. | The sponsor states: *'The 3 Phase II trials (1275148SCD2001, CNTO1275PBC2001, CNTO1275ARA2001) were previously included as additional pharmacovigilance activities in version 9.0 of the EU-RMP. Upon re-evaluation, it was determined that these trials were not specifically designed to address any specific safety concern due to the limited number of subjects. Therefore, these trials are no longer considered for inclusion as additional pharmacovigilance activities in EU-RMP version 11 and were removed accordingly.'* | This is acceptable. |
| 4. The studies referenced in the pharmacovigilance plan will generate safety data that will simply support the known | The sponsor states: *'A summary of forthcoming studies and anticipated dates for submission to the TGA is provided in the Stelara ASA, Sections* | This is acceptable. |

| Recommendation in RMP evaluation report | Sponsor's response | PMSB evaluator's comment |
|---|---|---|
| safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. To this end it is suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia. | *7 and 8. This tabular summary of the studies has previously been included in the EU RMP and is now being updated and added to the ASA. Note there are no ongoing studies in adults for the psoriasis or PsA indications.'* | |
| 5. The proposed Australian risk minimisation activities are similar to what was previously accepted for Stelara. At this time they continue to be acceptable. Nevertheless the sponsor should provide a table summarising the pharmacovigilance plan and risk minimisation plan proposed for Australia in the ASA. Wording pertaining to all the specified ongoing safety concerns in the proposed Australian PI and Consumer Medicine Information (CMI) should be included in the table. | The sponsor states: *'The Stelara ASA has been amended to incorporate the recommendation (Stelara ASA, Section 6).'* | Section 6 of the updated ASA only details the risk minimisation activities and is not inclusive of pharmacovigilance activities. It is recommended that the sponsor maintain this section of the ASA and also include a table summarising the pharmacovigilance and risk minimisation activities for all of the specified ongoing safety concerns and missing information proposed for Australia in a revised ASA, which should be submitted for review before this application is approved. |
| In regard to the proposed routine risk minimisation activities, several revisions to the draft PI were recommended to the Delegate. | The sponsor states: *'The recommendations made by the RMP evaluator in points 1, 3, and 4 were implemented in the Australian PI during the course of the evaluation of our previous submission, which was* | This generally acceptable. However, the Post-Market Surveillance Branch will be guided by the clinical evaluator and Delegate's assessment of the acceptability of the sponsor's |

| Recommendation in RMP evaluation report | Sponsor's response | PMSB evaluator's comment |
|---|---|---|
| | *approved 12 December 2013. Therefore, as this submission was made to the TGA in October 2013, they did not appear in the draft PI submitted with this application.*<br><br>*Regarding point 2, Janssen received the same question from TGA with the evaluation of the ustekinumab psoriasis 5-year data. In response to the question submitted at that time, the TGA accepted the rationale not to include these more restrictive warnings. Since the response submitted to TGA, Janssen has not identified any new safety concerns in pregnancy that might warrant us to reconsider the position.* | justification in relation to the important potential risk: 'Exposure during pregnancy' [the currently approved UK SmPC is more restrictive than the currently approved Australian PI. The Delegate was requested to consider the inclusion of this more restrictive statement to enhance safe use of these medicines]. |
| 7. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations. | The sponsor states: *'Janssen gives an assurance that the draft consumer medicine information document will be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.'* | This is acceptable. |

In their response to the TGA requests for further information the sponsor provided an updated ASA (Version 2.2, dated 22 August 2014). Key changes from the versions evaluated at First round are summarised below:

**Table 6: Key ASA changes**

| | |
|---|---|
| ASA | Medicine utilisation estimates have been updated to include 2013 figures.<br>Section 6: 'Summary Table of Risk Minimisation Measures for Australia' has been included.<br>Section 7: 'Summary of ongoing and completed studies and anticipated dates of submission in Australia' has been included.<br>Section 8: 'Summary of ongoing and completed pharmacoepidemiological studies and anticipated dates of submission in Australia' has been included. |

### Summary of recommendations

It is considered that the sponsor's response has not adequately addressed all of the issues identified in the RMP evaluation report

#### *Outstanding issues*

*Issues in relation to the RMP*

It was drawn to the Delegate's attention that the approved indications in the EU position Stelara as a second line therapy for the treatment of active psoriatic arthritis in adults rather than as first line therapy as sought for in Australia. Consequently the sponsor was asked to explain the reasons for this difference in indications between the EU and Australia in a revised ASA, as per the *Risk Management Plan (RMP) Questions & Answers (Version 1.3, October 2012)* on the TGA website. The sponsor has provided justification for these differences maintaining that ustekinumab was shown to be effective in both subjects who were exposed to previous DMARD therapy and those who were not exposed to previous DMARD therapy in the Phase III clinical studies. However, such information was not included in the updated ASA. The Post-Market Surveillance Branch will be guided by the clinical evaluator and Delegate's assessment of the acceptability of the sponsor's justification. Nevertheless it is reiterated that the sponsor should identify and explain the reasons for the difference in indications between the EU and Australia in a revised ASA before this application is approved.

The sponsor was asked to provide a table summarising the pharmacovigilance plan and risk minimisation plan proposed for Australia in the ASA. It was suggested that wording pertaining to all the specified ongoing safety concerns in the proposed Australian PI and CMI should be included in the table. The sponsor states: *'The Stelara ASA has been amended to incorporate the recommendation (Stelara ASA, Section 6).'* However, Section 6 of the updated ASA only details risk minimisation activities and is not inclusive of pharmacovigilance activities. It is recommended that the sponsor maintain this section of the ASA and also include a table summarising the pharmacovigilance and risk minimisation activities for all of the specified ongoing safety concerns and missing information proposed for Australia in a revised ASA which should be submitted for review before this application is approved.

Section 6: 'Summary Table of Risk Minimisation Measures for Australia' of the updated ASA indicates that there are no proposed routine risk minimisation measures for the important identified risk: 'Facial palsy'. It is recommended to the Delegate that the Adverse Effects section of the proposed Australian PI be amended to include 'Facial palsy' as an uncommon ADR similar to the current EU SmPC to enhance safe use of these medicines.

For the important potential risk: 'Exposure during pregnancy', it was noted the currently approved UK SmPC was more restrictive than the currently approved Australian PI. The Delegate was requested to consider including these more restrictive statements in the proposed Australian PI to enhance safe use of these medicines. The sponsor states:

> *Regarding point 2, Janssen received the same question from TGA with the evaluation of the ustekinumab psoriasis 5-year data* [information redacted]*. In response to the question submitted at that time, the TGA accepted the rationale not to include these more restrictive warnings. Since the response submitted to TGA, Janssen has not identified any new safety concerns in pregnancy that might warrant us to reconsider the position.*
>
> *Janssen's response to point 2 was provided below in Section 4.6.1. Note, this is the same response presented in the response document dated 18 November 2013 to TGA - Response to TGA Clinical Evaluation Report dated 13 Sept 2013-Part C - Comments on the Proposed PI related to Company Core Data Sheet (CCDS) updates from 5-year data in the psoriasis indication, Sections 3.2 and 3.2.1.*

The Post-Market Surveillance Branch will be guided by the clinical evaluator and Delegate's assessment of the acceptability of the sponsor's justification.

***Advice from the Advisory Committee on the Safety of Medicines (ACSOM)***

ACSOM advice was not sought for this submission.

***Suggested wording for conditions of registration***

*RMP*

The European Risk Management Plan (Version 11.0, dated 24 September 2014), with an Australian Specific Annex (Version 2.2, dated 22 August 2014) to be revised as agreed with the TGA, must be implemented.

# VI. Overall conclusion and risk/benefit assessment

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

### Quality

The submission did not require quality data.

### Nonclinical

The submission includes update to the 'Pharmacology: Mechanism of action' section of the Product Information (PI) for which the supporting data have been evaluated by the TGA nonclinical area.

### Clinical

The dossier included pharmacokinetic (PK) data from the PsA studies (including population PK analysis) and pharmacodynamic (PD) data for which please see the clinical evaluation report (CER).

The proposed use in PsA is based on one Phase II dose finding study and two pivotal Phase III efficacy studies. These are briefly discussed below. The clinical evaluator recommends approval with a modified indication which does not include claim of inhibition of

structural damage and proposes second line use in patients who respond inadequately to conventional (non-biologic) DMARDs.

### Dose selection

The relevant study is C0743T10 which was a placebo-controlled Phase II study in adult patients with PsA with two treatment arms (USK 90 mg SC at Weeks 0, 1, 2 and 3 arm (n=76) and placebo arm (n=70)) with primary efficacy endpoint assessment at 12 weeks. The patients in placebo group crossed over to receive USK at weeks 12 and 16 with overall follow up to 36 weeks. The drug manufacturer added a filtration process during the course of the study which resulted in reducing the fill volume from 1.0 mL (90 mg USK) to 0.70 mL (63 mg USK). The first 36 patients in the study (17 in the USK group) were randomised prior to the change and received the intended USK 90 mg x 4 injections. The USK patients randomised after the manufacturing change (n=59), received USK 63 mg x 4 injections, whereas the crossover placebo patients also received USK 63 mg dose (n=57) at Week 12 (n=57) and Week 16 (n=55). In the Delegate's view, the results of this study are not interpretable and did not meaningfully add to decision making for appropriate dose selection for studying in the PsA population. The principal dose, that is, 45 mg was not examined in this study.

### Pivotal clinical studies

The two pivotal Phase III studies are PSUMMIT I and PSUMMIT II. Both were identically designed and examined same dosing regimens and clinical outcomes. The only difference was that PSUMMIT I population consisted entirely of anti-TNF naïve patients, whereas PSUMMIT II population eligibility criteria (through a protocol amendment) allowed inclusion of anti-TNF exposed patients in addition to naïve patients.

Both trials were to be analysed individually with to efficacy and safety. However, the effect of USK on structural damage was to be examined based on pooled data from both studies.

The trials were randomised, double-blind, placebo-controlled and in adult patients with active PsA (see Attachment 2 for details) despite previous or current treatment with NSAID and/or conventional non-biologic DMARDs.

The patients were randomised 1:1:1 to receive treatment with USK 45 mg, USK 90 mg, or placebo by SC route at Weeks 0 and 4 (loading doses), followed by q12w. The placebo group patients crossed-over to active treatment with USK 45 mg at Weeks 24 and 28 (loading dose), followed by q12w dosing thereafter.

The trial design also allowed for 'early escape' (EE) in poor responders. At Week 16, patients with < 5% improvement from baseline in both tender & swollen joint counts were eligible to enter EE in a double-blind fashion without re-randomisation. For EE patients, treatment after Week 16 remained double-blinded.

In PSUMMIT I, patients randomised to placebo who qualified for EE at Week 16 switched to USK 45 mg at Weeks 16, 20 and 28, followed by a q12w through to Week 88. The remaining placebo patients crossed over to USK 45 mg with dosing at Weeks 24 and 28 followed by q12w through to Week 88. The patients randomised to USK 45 mg who qualified for EE switched to 90 mg at Week 16 followed by q12w dosing with the last dose at Week 88. The patients randomised to USK 90 mg who qualified for EE continued at the same dose level. The patients were to be followed up to Week 100 for efficacy and Week 108 for safety. Same procedure was adopted in PSUMMIT II where the duration of study was 60 weeks.

Methotrexate (MTX) up to 25 mg/week (oral or parenteral) was permitted at entry (stable for preceding 4 weeks) and during the study. All NSAID use was allowed. The patients were also able to continue low dose CS up to a maximum oral dose of 10 mg/day

prednisone or equivalent if they had been receiving a stable dose for at least 2 weeks. The participating patients were also required to have active psoriatic skin lesions or documented history of plaque psoriasis. Phototherapy and/or topical agents for psoriasis (including low potency topical CS) were also allowed.

Randomization was stratified by site, body weight (≤ 100 kg or > 100 kg) and baseline MTX use (yes/no). The randomisation method was minimisation with a biased-coin assignment in a ratio of 1:1:1.

In PSUMMIT I, a total of 615 eligible patients were randomised to the 3 groups (USK 45 mg n = 205; USK 90 mg n = 204; placebo n = 206). At Week 16, 58/205 (28.3%) placebo group patients, 36/205 (17.6%) USK 45 mg patients and 26/204 (12.7%) USK 90 mg patients met the EE criteria. A total of 560/615 (91.1%) completed 52 weeks of treatment follow-up in the PSUMMIT I Study. The primary efficacy results were reported at Week 24.

In PSUMMIT II, a total of 312 eligible patients were randomised to 3 treatment groups (USK 45 mg group n = 103; USK 90 mg group n = 105; placebo n = 104). At Week 16, 31/104 (29.8%) placebo patients, 20/103 (19.4%) USK 45 mg patients and 22/104 (21.2%) USK 90 mg patients met EE criteria. A total of 238/312 (76.3%) completed 52 weeks of treatment follow-up in the PSUMMIT II Study. The primary results were reported at 24 weeks.

Overall, the treatment groups were comparable at baseline in both studies. The primary efficacy assessment was at 24 weeks. The dossier contained efficacy/safety data to 52 weeks.

In PSUMMIT I, 48.1% (296/615) patients continued MTX therapy. The median weekly dose of concurrent MTX in all 3 groups was 15 mg. In PSUMMIT II, 49.7% (155/312) patients continued MTX therapy. The median weekly dose of concurrent MTX was 17.5 mg (placebo group), 15 mg (USK 45 mg group) and 15 mg (USK 60 mg group). A total of 180/312 (58%) patients in PSUMMIT II had a prior history of receiving anti-TNF drugs (59.6% (62/104) in placebo group; 56.3% (58/103) in USK 45 mg group; 57.1% (60/105) in USK 90 mg group). The 3 most commonly used anti-TNF drugs were etanercept (36.9%; 115/312), adalimumab (32.4%; 101/312) and infliximab (30.8%; 96/312). A small proportion of patients had history of golimumab use (5.1%; 16/312) and 3/312 (1%) patients had history of certolizumab use. Three patients also had prior exposure to anakinra (1 in placebo group and 2 in USK 90 mg group). The rate of previous and concurrent MTX, NSAID and CS use was similar between anti TNF experienced and naïve patients.

### *Results – PSUMMIT I*

*Week 24 – ACR data*

The onset of response was observed as early as Week 4 when the ACR20 response rate was 11.8%, 17.6% and 20.0% in placebo, USK 45 mg and USK 90 mg groups respectively. The unconfounded placebo-controlled comparison was at Week 16 when the ACR20 response rate was 21.9%, 34.3% and 44.7% in the 3 treatment groups respectively.

At Week 24, ACR20 response rate in USK 45 mg group was 42.4% (87/205) compared to 22.8% (47/206) in placebo group. The treatment difference was 19.6% (95% Confidence Interval (CI) 10.8% to 28.5%).

At Week 24, ACR20 response rate in USK 90 mg group was 49.5% (101/204) compared to 22.8% (47/206) in placebo group. The treatment difference was 26.7% (95%CI 17.8% to 35.6%).

Various sensitivity analyses supported the primary analysis. The trends in all individual components were consistent with the overall composite endpoint.

The ACR20 response rates at Week 24 in patients taking MTX at baseline versus not taking MTX were 26.0% versus 20.0% (placebo), 43.4% versus 41.5% (45 mg), and 45.5% versus 53.4% (90 mg).

The ACR20 response rates at Week 24 in patients with body weight ≤ 100 kg versus > 100 kg were 25.3% versus 15.4% (placebo), 43.8% versus 38.5% (45 mg) and 50.6% versus 46.0% (90 mg).

At Week 24, the ACR50 response rate was 8.7% (18/206), 24.9% (51/205) and 27.9% (57/204) in placebo, USK 45 mg, USK 90 mg groups respectively.

The ACR50 response rates at Week 24 in patients receiving MTX at baseline versus not receiving MTX were 8.3% versus 9.1% (placebo), 23.2% versus 26.4% (45 mg) and 26.7% versus 29.1% (90 mg)).

The ACR50 response rates at Week 24 in patients with body weight ≤ 100 kg versus > 100 kg were 9.1% versus 7.7% (placebo), 24.8% versus 25.0%, (45 mg) and 31.2% versus 18.0% (90 mg).

At Week 24, the ACR70 response rate was 2.4% (5/206), 12.2% (25/205) and 14.2% (29/204) in placebo, USK 45 mg and USK 90 mg groups respectively.

The ACR70 response rates at Week 24 in patients receiving MTX at baseline versus not receiving MTX were 2.1% versus 2.7% (placebo), 11.1% versus 13.2% (45 mg) and 12.9% versus 15.5% (90 mg).

The ACR70 response rates at Week 24 in patients with body weight ≤ 100 kg versus > 100 kg were 3.2% versus 0.0% (placebo), 13.1% versus 9.6% (45 mg) and 16.9% versus 6.0% (90 mg).

*52 weeks – ACR data*

At Week 52, for patients receiving USK 45 mg (n = 194), the ACR20, ACR50 and ACR70 response rates were 55.7% (108/194), 31.4% (61/194) and 18.0% (35/194) respectively.

At Week 52, for patients receiving USK 90 mg (n = 189), ACR20, ACR50 and ACR70 response rates were 60.3% (114/189), 37.0% (70/189) and 21.2% (40/189) respectively.

At Week 52, for patients initially randomised to placebo group and escaped to USK 45 mg (Week 16) or switched to USK 45 mg (Week 24) (n = 184), ACR20, ACR50 and ACR70 response rates were 65.2% (120/184), 38.0% (70/184) and 16.3% (30/184) respectively.

At Week 52, response rates in patients receiving MTX at baseline versus not receiving MTX were 54.3% versus 56.9% (ACR20), 27.2% versus 35.3% (ACR50) and 17.4% versus 18.6% (ACR70) in USK 45 mg group.

At Week 52, response rates in patients receiving MTX at baseline versus not receiving MTX were 57.3% versus 63.4% (ACR20), 30.2% versus 44.1% (ACR50) and 17.7% versus 24.7% (ACR70) in USK 90 mg.

At Week 52, response rates in patients with body weight ≤ 100 kg versus > 100 kg were 61.6% versus 37.5%, (ACR20), 36.3% versus 16.7% (ACR50), and 21.2% versus 8.3% (ACR70) in USK 45 mg group.

At Week 52, response rates in patients with body weight ≤ 100 kg versus > 100 kg were 62.5% versus 53.3% (ACR20), 39.6% versus 28.9% (ACR50) and 23.6% versus 13.3% (ACR70) in USK 90 mg group.

*Other results*

At baseline, overall 71.7% (441/615) patients reported with enthesitis. At 24 weeks, the proportion of patients with ongoing enthesitis was 68.6% (96/140) and 60.8% (90/148)

in USK 45 mg and USK 90 mg groups respectively compared with 81.0% (111/137) in placebo group.

At 52 weeks, among patients with enthesitis at baseline, the proportion of patients with ongoing enthesitis was 55.6% and 54.2% in USK 45 mg and USK 90 mg groups respectively. In the placebo to USK 45 mg dose switch group, the proportion of patients with enthesitis at week 52 was 51.6%.

At baseline, overall 48.1% (296/615) patients were reported with at least 1 digit dactylitis. At Week 24, the proportion of patients with ongoing dactylitis in 1 or more digits was 56.6% (56/99) and 55.8% (53/95) in USK 45 mg and USK 90 mg groups respectively compared with 76.1% (70/92) in placebo group.

At Week 52, among patients with dactylitis at baseline, the proportion of patients with ongoing dactylitis was 39.2% and 46.2% in the USK 45 mg and USK 90 mg groups respectively. In the placebo to USK 45 mg dose switch group, the proportion of patients with dactylitis at Week 52 was 40.7%.

For additional secondary outcomes (HAQ, PASI, PsARC, BASDAI, DAS28, SF26, DLQI) please see Attachment 2. In general, the results were consistent a beneficial effect on treatment with ustekinumab.

***Results - PSUMMIT II***

*Week 24 – ACR data*

As in the PSUMMIT I study, the onset of response was noticeable as early as Week 4 when the ACR20 response rate was 8.9%, 15.7% and 17.3% in placebo, USK 45 mg and USK 90 mg groups respectively. The unconfounded placebo-controlled comparison was at Week 16 when the ACR20 response rate was 13.4%, 30.4% and 30.0% in the 3 treatment groups respectively.

At Week 24, ACR20 response rate was 43.7% (45/103) in USK 45 mg versus 20.2% (21/104) in placebo group. The treatment difference was 23.5% (95%CI 11.2% to 35.8%).

At Week 24, ACR20 response rate was 43.8% (46/105) in USK 90 mg group versus 20.2% (21/104) in placebo group. The treatment difference was 23.6% (95%CI 11.4% to 35.8%).

Various sensitivity analyses supported the primary analysis. The trends in all individual components were consistent with the overall composite endpoint.

The Week 24 ACR20 response rate in patients on MTX at baseline versus not taking MTX was 50.0% versus 36.7% (45 mg), 40.4% versus 47.2% (90 mg) and 28.6% versus 12.7% (placebo).

The Week 24 ACR20 response rate in patients weighing ≤ 100 kg versus > 100 kg was 43.2% versus 44.8% (45 mg), 46.6% versus 38.7% (90 mg) and 23.0% versus 13.3% (placebo).

The Week 24 ACR20 response rate in anti-TNF naïve patients versus anti-TNF experienced patients was 53.5% versus 36.7% (45 mg), 55.3% versus 34.5% (90 mg) and 28.6% versus 14.5% (placebo).

At Week 24, ACR50 response rate was 6.7% (7/104), 17.5% (18/103) and 22.9% (24/105) in placebo, USK 45 mg and USK 90 mg groups respectively.

The Week 24 ACR50 response rate in patients on MTX at baseline versus not taking MTX was 18.5% versus 16.3% (45 mg), 23.1% versus 22.6% (90 mg) and 8.2% versus 5.5% (placebo).

The Week 24 ACR50 response rate in patients weighing ≤ 100 kg at baseline versus > 100 kg was 20.3% versus 10.3% (45 mg), 28.8% versus 9.7% (90 mg) and 8.1% versus 3.3% (placebo).

The Week 24 ACR50 response rate in anti-TNF naïve patients versus anti-TNF experienced patients was 20.9% versus 15.0% (45 mg), 31.9% versus 15.5% (90 mg) and 7.1% versus 6.5% (placebo).

At Week 24, the ACR70 response rate was 2.9% (3/104), 6.8% (7/103) and 8.6% (9/105) in placebo, USK 45 mg and USK 90 mg groups respectively.

The Week 24 ACR70 response rate in patients on MTX at baseline versus not taking MTX was 7.4% versus 6.1% (45 mg), 5.8% versus 11.3% (90 mg) and 4.1% versus 1.8% (placebo).

The Week 24 ACR70 response rate in patients weighing ≤ 100 kg versus > 100 kg was 8.1% versus 3.4% (45 mg group), 11.0% versus 3.2% (90 mg group) and 4.1% versus 0.0% (placebo group).

The Week 24 ACR70 response rate in anti-TNF naïve patients versus anti-TNF experienced patients was 9.3% versus 5.0% (45 mg group), 12.8% versus 5.2% (90 mg group) and 4.8% versus 1.6% (placebo).

*52 weeks – ACR data*

At Week 52, for patients in USK 45 mg group (n = 94), ACR20, ACR50 and ACR70 response rates were 46.8% (44/94), 27.7% (26/94) and 12.8% (12/94) respectively.

At Week 52, for patients in USK 90 mg (n = 95), ACR20, ACR50 and ACR70 response rates were 48.4% (46/95), 26.3% (25/95) and 17.9% (17/95) respectively.

At Week 52, for patients initially randomised to placebo group and escaped to USK 45 mg (Week 16) or switched to USK 45 mg (Week 24) (n = 77), ACR20, ACR50 and ACR70 response rates were 55.8% (43/77), 28.6% (22/77) and 15.6% (12/77) respectively.

At Week 52, response rates in patients receiving MTX at baseline versus not receiving MTX were 46.0% versus 47.7% (ACR20), 26.0% versus 29.5% (ACR50) and 12.0% versus 13.6% (ACR70) in USK 45 mg group.

At Week 52, response rates in patients receiving MTX at baseline versus not receiving MTX were 56.5% versus 40.8% (ACR20), 28.3% versus 24.5% (ACR50) and 17.4% versus 18.4% (ACR70) in USK 90 mg group.

At Week 52, response rates in patients with body weight ≤ 100 kg versus > 100 kg were 49.3% versus 40.7% (ACR20), 31.3% versus 18.5% (ACR50) and 14.9% versus 7.4% (ACR70) in the USK 45 mg group.

At Week 52, response rates in patients with body weight ≤ 100 kg versus > 100 kg were 53.7% versus 35.7% (ACR20), 29.9% versus 17.9% (ACR50) and 22.4% versus 7.1% (ACR70) in the USK 90 mg group.

At Week 52, response rates in patients previously exposed to anti-TNF agents versus not exposed were 37.0% versus 60.0% (ACR20), 18.5% versus 40.0% (ACR50) and 5.6% versus 22.5% (ACR70) in the USK 45 mg group.

At Week 52, response rates in patients previously exposed to anti-TNF agents versus not exposed were 40.7% versus 58.5% (ACR20), 20.4% versus 34.1% (ACR50) and 7.4% versus 31.7% (ACR70) in the USK 90 mg group.

*Other results*

At baseline, overall 70.8% (221/312) patients were reported with enthesitis. At 24 weeks, the proportion of patients with ongoing enthesitis was 75.7% (53/70) and 70.0% (49/70) in the USK 45 mg and USK 90 mg groups respectively compared with 88.2% (60/68) in the placebo group.

At 52 weeks, among patients with enthesitis at baseline, the percentage of patients with ongoing enthesitis was 75.8% and 57.7% in USK 45 mg and USK 90 mg groups respectively. In the placebo to USK 45 mg dose switch group, the percentage of patients with enthesitis at week 52 was 67.9%.

At baseline, overall 40.7% (127/312) patients were reported with at least 1 digit with dactylitis. At Week 24, the proportion of patients with ongoing dactylitis in 1 or more digits was 65.2% (30/46) and 57.9% (22/38) in USK 45 mg and USK 90 mg groups respectively compared with 75.8% (25/33) in placebo group.

At Week 52, among patients with dactylitis at baseline, the percentage of patients with ongoing dactylitis was 50.0% in both USK dose groups. In the placebo to USK 45 mg dose switch group, the proportion of patients with dactylitis at week 52 was 33.3%.

For additional secondary outcomes (HAQ, PASI, PsARC, BASDAI, DAS28, SF26, DLQI) please see CER, Attachment 2. In general, the results were consistent with a beneficial effect on treatment with ustekinumab.

### *Radiographic assessment*

The effect of USK therapy on the rate of progression of joint damage was assessed by serial plain radiographs of hands and feet taken at baseline, Week 24 and Week 52 or at the time of study discontinuation (unless available from previous 8 weeks) regardless of 'early escape' status in both pivotal studies. The pooled dataset consisted of 927 patients (747 anti-TNF treatment naïve and 180 anti-TNF experienced). These included 310 in placebo group (62 anti-TNF experienced), 308 USK 45 mg group (60 anti-TNF experienced) and 309 USK 90 mg group (58 anti-TNF experienced).

The vdH-S modified for PsA was used to assess structural joint damage and its progression.[21] At baseline the overall score was 28.79 (SD 49.85) in the sample population indicating early mild degree of structural damage:

**Table 7: Summary of total modified van der Heijde-Sharp scores at baseline; randomised subjects in CNTO1275PSA3001 and CNTO1275PSA3002 studies.**

| | | Ustekinumab | | | |
|---|---|---|---|---|---|
| | Placebo | 45 mg | 90 mg | Combined | Total |
| Subjects randomized | 310 | 308 | 309 | 617 | 927 |
| Total score | | | | | |
| N | 306 | 303 | 300 | 603 | 909 |
| Mean (SD) | 28.01 (55.771) | 30.40 (50.688) | 27.97 (42.137) | 29.19 (46.607) | 28.79 (49.853) |
| Median | 9.50 | 11.50 | 10.50 | 11.00 | 11.00 |
| IQ range | (3.00; 29.50) | (3.50; 33.50) | (3.50; 34.50) | (3.50; 34.00) | (3.00; 32.64) |
| Range | (0.0; 500.5) | (0.0; 310.3) | (0.0; 346.0) | (0.0; 346.0) | (0.0; 500.5) |

At Week 24, the change in total score from baseline to Week 24 was 0.40 (SD 2.26) in the combined USK group compared to 0.97 (SD 3.85) in the placebo group as shown below:

[21] PsA modified vdH-S score is the sum of the joint space narrowing (JSN) score plus the erosion score (ES) and has a range of 0-528; higher score indicates more radiographic damage, and a positive change represents radiographic progression. Total score consists of composite of JSN (range 0-208; 26 sites (20 joints in hands and 6 in feet) on each side of the body scored from 0-4 for each site) and the ES (range 0-320; 26 sites (20 joints in hands and 6 in feet) on each side of the body). Erosions in each hand are scored from 0 (no erosion) to 7 (gross osteolysis). However, for total score calculation scores of 6 (pencil-in-cup abnormality) and 7, a maximum score of 5 is assigned.

**Table 8: Summary of total modified van der Heijde-Sharp scores at Week 24; randomised subjects in CNTO1275PSA3001 and CNTO1275PSA3002 studies.**

| | | Ustekinumab | | |
|---|---|---|---|---|
| | Placebo | 45 mg | 90 mg | Combined |
| Subjects randomized | 310 | 308 | 309 | 617 |
| Change from baseline | | | | |
| N | 310 | 308 | 309 | 617 |
| Mean (SD) | 0.97 (3.852) | 0.40 (2.110) | 0.39 (2.403) | 0.40 (2.260) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| IQ range | (0.00; 1.00) | (0.00; 0.50) | (0.00; 0.50) | (0.00; 0.50) |
| Range | (-3.0; 58.0) | (-9.5; 14.0) | (-6.0; 27.0) | (-9.5; 27.0) |
| p-value[a] | | 0.017 | <0.001 | <0.001 |
| p-value[b] | | 0.018 | < 0.001 | < 0.001 |

[a] Based on re-randomization test.
[b] Based on van der Waerden test.

At Week 52, the change in total score from baseline to Week 52 was 0.62 (SD 3.19) in the combined USK group compared to 1.15 (SD 5.41) in the placebo group as shown below:

**Table 9: Summary of total modified van der Heijde-Sharp scores at Week 52; randomised subjects in CNTO1275PSA3001 and CNTO1275PSA3002 studies.**

| | | Ustekinumab | | |
|---|---|---|---|---|
| | Placebo → 45 mg [a] | 45 mg | 90 mg | Combined |
| Subjects randomized | 269 | 308 | 309 | 617 |
| Change from baseline | | | | |
| N | 269 | 308 | 309 | 617 |
| Mean (SD) | 1.15 (5.409) | 0.58 (2.597) | 0.65 (3.684) | 0.62 (3.185) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| IQ range | (0.00; 1.00) | (0.00; 1.00) | (0.00; 0.50) | (0.00; 0.50) |
| Range | (-8.0; 76.5) | (-11.5; 15.5) | (-8.0; 42.9) | (-11.5; 42.9) |

[a] Subjects who did not receive ustekinumab are excluded.

The two studies were also analysed individually and indicated (24 weeks data) treatment effect in favour of USK over placebo in PSUMMIT I but no treatment effect with USK over placebo in PSUMMIT II as shown below:

**Table 10: Summary of change from baseline in total modified van der Heijde-Sharp scores at Week 24: randomised subjects in CNTO1275PSA3001**

| | | Ustekinumab | | |
|---|---|---|---|---|
| | Placebo | 45 mg | 90 mg | Combined |
| Subjects randomized | 206 | 205 | 204 | 409 |
| Change from baseline | | | | |
| N | 206 | 205 | 204 | 409 |
| Mean (SD) | 1.20 (4.520) | 0.28 (1.943) | 0.17 (1.446) | 0.23 (1.712) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| IQ range | (0.00; 1.50) | (0.00; 0.50) | (-0.25; 0.50) | (0.00; 0.50) |
| Range | (-3.0; 58.0) | (-9.5; 13.0) | (-6.0; 6.5) | (-9.5; 13.0) |
| p-value | | 0.001 | < 0.001 | < 0.001 |

**Table 11: Summary of change from baseline in total modified van der Heijde-Sharp scores at Week 24: randomised subjects in CNTO1275PSA3002**

| | | Ustekinumab | | |
|---|---|---|---|---|
| | Placebo | 45 mg | 90 mg | Combined |
| Subjects randomized | 104 | 103 | 105 | 208 |
| Change from baseline | | | | |
| N | 104 | 103 | 105 | 208 |
| Mean (SD) | 0.51 (1.875) | 0.66 (2.398) | 0.81 (3.571) | 0.73 (3.040) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| IQ range | (0.00; 0.50) | (0.00; 1.00) | (0.00; 0.50) | (0.00; 0.50) |
| Range | (-3.0; 10.5) | (-8.1; 14.0) | (-2.5; 27.0) | (-8.1; 27.0) |
| p-value | | 0.605 | 0.965 | 0.755 |

A post hoc analysis of anti-TNF naïve subgroup of the PSUMMIT II study indicated that patients with higher inflammatory activity at baseline (CRP ≥ 10 mg/L) had less X-ray progression at 24 weeks, particularly with the 90 mg dose. In the anti-TNF naïve subgroup

with baseline CRP < 10 mg/L in this study, no treatment effect versus placebo was observed. Furthermore, in anti-TNF experienced patients in this study, no treatment effect versus placebo was observed regardless of baseline CRP reading. The sponsor also submitted two additional post hoc analyses based on modelling of the X-ray progression using the results of the two anti-TNF naïve populations from PSUMMIT I and II studies (see CER, Attachment 2).

The sponsor also provided Week 100 radiographic results for PSUMMIT I Study. The cumulative change from baseline, in the total modified vdH-S, to Week 100 in PSUMMIT I was as follows (from sponsor's response to the First Round CER):

**Table 12: Week 100 radiographic results for PSUMMIT I Study. The cumulative change from baseline, in the total modified vdH-S.**

| | | Ustekinumab | | |
|---|---|---|---|---|
| | Placebo → 45 mg [a] | 45 mg | 90 mg | Combined |
| Subjects randomized | 189 | 205 | 204 | 409 |
| Week 52 | | | | |
| Change from baseline | | | | |
| N | 189 | 205 | 204 | 409 |
| Mean (SD) | 1.49 (8.182) | 0.48 (2.471) | 0.55 (2.965) | 0.51 (2.726) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| IQ range | (0.00; 1.00) | (0.00; 1.00) | (0.00; 1.00) | (0.00; 1.00) |
| Range | (-4.5; 104.5) | (-10.5; 12.4) | (-15.5; 17.5) | (-15.5; 17.5) |
| Week 100 | | | | |
| Change from baseline | | | | |
| N | 189 | 205 | 204 | 409 |
| Mean (SD) | 2.26 (12.578) | 0.95 (3.816) | 1.18 (5.052) | 1.07 (4.471) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| IQ range | (0.00; 1.00) | (0.00; 1.00) | (0.00; 1.00) | (0.00; 1.00) |
| Range | (-4.2; 161.0) | (-11.0; 31.0) | (-18.0; 41.0) | (-18.0; 41.0) |

[a] Subjects who did not receive ustekinumab are excluded.

At Week 100 (PSUMMIT I data), the change in total score from baseline to Week 100 was 1.07 (SD 4.47) in the combined USK group compared to 2.26 (SD 12.58) in the placebo switch group. The cumulative changes in total score through to Week 100 were slow in all groups. The interquartile (IQ) range (representing middle 50% of the sample population) was 0 to 1 in all groups. The total range indicated that the higher quarter (75 to 100) deteriorated much more (range -4.2 to 161) in the placebo switch group compared to the two USK groups (range -11 to 31 and -18 to 41). However, this persisting comparative disadvantage in the switch group at Week 100 due to initial 16 weeks of placebo is surprising.

### Clinical safety

A total of 914 patients were exposed to USK in the three PsA studies. All administrations were by SC route. Of these, 76% (692/914) were exposed for at least 6 months and 23% (213/914) for at least one year. Both of the proposed dose levels in PsA (45 mg and 90 mg) had more than 300 patients exposed for at least 6 months. The safety data from other indications (psoriasis and Crohn's disease) were also provided in support of the proposed use in PsA. Four psoriasis trials have now followed patients for up to 5 years. In terms of long-term safety, 307 patients in 45 mg dose cohort and 432 patients in 90 mg dose cohort have received USK for at least 5 years. In two Phase II trials in Crohn's disease, a total of 158 patients have been exposed to USK for at least 6 months with intravenous doses up to 6 mg/kg.

In the three PsA studies, approximately half of the patients in the dataset received concurrent MTX, more than 75% were taking concomitant NSAID, and about 1 out of 6 were taking concurrent low dose oral corticosteroid. In the PSUMMIT II trial, 180 patients had received prior biologic therapy, mainly with anti-TNF therapy.

The incidence any AEs was 47.9%, 48.4% and 49.4% in placebo, USK 45 mg and USK 90 mg groups respectively during the placebo controlled period (16 weeks) in the two pivotal Phase III studies based on average duration of follow up of 15.79 weeks, 16.15 weeks and 16.08 weeks in the three groups respectively.

The incidence SAEs was 2.9%, 1.3% and 1.3% in placebo, USK 45 mg and USK 90 mg groups respectively during the placebo-controlled period (16 weeks) in the 2 pivotal Phase III studies.

The incidence infections was 22.0%, 20.8% and 21.4% in placebo, USK 45 mg and USK 90 mg groups respectively during the placebo controlled period (16 weeks) in the two pivotal Phase III studies

Infection was the most common AE in PsA studies and occurred at a slightly higher frequency in the USK treatment groups versus control during placebo (12 to 16 weeks in one Phase II and two Phase III studies respectively). Some gastrointestinal AEs were also more common in USK treated patients, particularly diarrhoea and nausea. The patients weighing > 100 kg had a higher incidence of Overall and Infection related AEs. SAEs including serious infection related events were reported in a low proportion of USK-treated patients in both pivotal trials (< 3%). No patients developed reactivation of latent tuberculosis and no other significant opportunistic infections were reported in the dataset.

No acute systemic hypersensitivity reactions have been reported in the three PsA trials. One case of rebound psoriasis was reported in a USK treated patient in the two pivotal studies. No deaths were reported in the three PsA studies.

A total of 8 major cardiovascular events were reported in USK treated patients. These included 5 myocardial infarcts, 2 cerebrovascular accidents and one atrial fibrillation.

Three patients developed malignancies in the PsA studies (two reports in PSUMMIT II and one in the Phase II study). Two were non-melanoma skin cancer and one was breast cancer.

The combined PsA dataset (one Phase II and two Phase III studies) comprised of 110PY, 96PY and 113PY of follow up in the placebo, USK 45 mg and USK 90 mg groups respectively during the controlled period and 143PY, 256PY and 295PY of follow up to the end of reporting period. No deaths were reported.

The incidence of serious infection was 0.70/100PY, 1.17/100PY and 0.68/100PY in placebo, USK 45 mg and USK 90 mg groups, respectively, through to the end of reporting period.

The incidence of adjudicated Major Adverse Cardiovascular Events (MACE) was 0.70/100PY, 0.78/100PY and 0.34/100PY in placebo, USK 45 mg and USK 90 mg groups, respectively, through to the end of reporting period.

The incidence of neoplasm (malignant) was 0.00/100PY, 0.00/100PY and 0.68/100PY in placebo, USK 45 mg and USK 90 mg groups, respectively, through to the end of reporting period.

No significant abnormalities of laboratory values (including hepatic transaminases) compared with placebo have been associated with USK in the PsA study program. Two cases of significant thrombocytopenia in USK treated patients and mild-moderate asymptomatic lymphopenia were also reported.

The incidence of PsA treated patients developing anti-USK antibodies was 7% to 9% at 52 to 60 weeks using the combined USK treated datasets in the PSUMMIT studies.

These safety outcomes were consistent with the known profile of USK in the approved indication of psoriasis. The pharmacovigilance activities will need to continue to target the

occurrences of opportunistic infections, MACE and malignancies (including non-melanoma skin cancers).

At the time of submission in Australia, no postmarketing data for the PsA indication was available. As of June 30, 2012, a number of PSURs have been submitted. Hypersensitivity reactions (including rash and urticaria post-injection) and serious allergic reactions (including anaphylaxis and angioedema) have been identified from spontaneous ADR reports. The other safety concerns under surveillance are serious infection (including tuberculosis and salmonella), malignancies, major adverse cardiovascular events, neurologic disorders (including facial palsy) and pregnancy outcomes. In the PsA studies to date, three patient pregnancies and two partner pregnancies have been reported. No further information on the outcome of each of these pregnancies has been provided.

## Risk management plan

EU-RMP Version 11.0 (dated 24 September 2013) with an Australian Specific Annex (ASA) Version 2.1 (dated 18 December 2013) applies to this submission and will be a condition of registration. ACSOM advice was not sought by the TGA for this submission. The sponsor provided an updated version of the ASA (version 2.2; dated 22 August 2014) after the first round evaluation. Agreement with Post-Market Surveillance Branch at the TGA is yet to be confirmed.

## Risk-benefit analysis

### Delegate's conclusion and recommendation

1. Ustekinumab was first approved in Australia in 2009 for the treatment of plaque psoriasis. The current submission is extension of indication to treat psoriatic arthritis (PsA) in adult patients with moderately severe, active disease.
2. The dose selection has been extrapolated from the currently approved dosing regimen for plaque psoriasis. No systematic investigation of dosing regimen was carried out for the psoriatic arthritis indication. Both dosing regimens (45 mg SC at 0 and 4 weeks followed by q12 w and alternative 90 mg dosing in patients over 100 kg body weight) currently approved in plaque psoriasis were examined in two Phase III studies in patients with PsA. This is considered clinically justifiable.

   Advice from the TGA's Advisory Committee on Prescription Medicines (ACPM) is requested.
3. The two pivotal clinical trials provided evidence of moderate efficacy (placebo-controlled treatment difference for ACR20: 19.6% [95%CI 10.8-28.5%] and 26.7% [95%CI 17.8-35.6%] with USK 45 mg and USK 90 mg respectively in PSUMMIT I; 23.5% [95%CI 11.2-35.8%] and 23.6% [95%CI 11.4-35.8%] with USK 45 mg and USK 90 mg respectively in PSUMMIT II) for control of signs and symptoms after 24 weeks of treatment. The effect was maintained to 52 weeks. In general, the overall treatment effect with both doses (45 mg versus 90 mg) was similar but was not formally statistically tested.
4. In previous clinical trials with the currently available biologic DMARDs, the ACR20 response rates at 24 weeks (based on approved prescribing information) have been in the range 22% versus 38% (placebo versus anakinra), 15% versus 57% (placebo versus adalimumab), 13% versus 50% (placebo versus etanercept), 16% versus 54% (placebo versus infliximab), 24% versus 64% (placebo versus certolizumab) and 12% versus 52% (placebo versus golimumab). A head to head trial with a comparator biologic DMARD has not been provided and a judgement of relative efficacy is not

possible. A relatively higher placebo effect and moderate USK effect was observed in USK PsA trials compared to the existing biological DMARDs.

5. The effect of USK on enthesitis and dactylitis was less pronounced. Additional secondary outcomes examining the effect of USK on accompanying skin psoriasis, patient and physician assessments, health outcomes and quality of life outcomes were also consistent with a beneficial effect with USK treatment. The data support use of USK with or without methotrexate (monotherapy). About half of the participating patients in the PsA clinical trials were taking MTX and the outcomes were similar to those who were not taking MTX.

6. The clinical trials population in the two pivotal studies consisted of adult patients who had active PsA despite current or previous DMARD and/or NSAID therapy. The previously used DMARD was mainly MTX. As noted above, USK use as monotherapy (without MTX) is also supported based on the submitted data. However, it is important that the qualifying criteria for patient participation in clinical trials be reflected in the therapeutic indication ('*in patients where response to previous non-biological DMARD therapy has been inadequate'*) to ensure appropriate selection of patients in clinical use of USK in PsA patients.

   Advice from ACPM is requested.

7. The data also suggest use of 90 mg dose as 'alternative' dose in patients with body weight over 100 kg ('recommended dose is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg administered over Weeks 0 and 4, then every 12 weeks thereafter may be used in patients with a body weight greater than 100 kg'). This is supported, although the more consistent higher effect with 90 mg compared to 45 mg was seen with respect to PASI 75/90/100 rather than ACR 20/50/70.

   Advice from ACPM is requested.

8. Note that the US label specifies 90 mg as the recommended dose *'for patients with co-existent moderate-to-severe plaque psoriasis weighing > 100 kg (220 lbs)'*.

9. The EU approval for 90 mg dose notes '*For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy*.'

10. The safety outcomes were consistent with the known adverse effects profile of USK in plaque psoriasis. An ongoing surveillance with respect to serious infections, malignancies and major adverse cardiovascular events will be required.

11. Dose adjustment or treatment discontinuation in poor responders was not studied in the PsA clinical studies. The EU approval includes advice that '*consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment*'. This is also considered justified for inclusion in the Australian prescribing information.

    Advice from ACPM is requested.

12. The inhibition of structural joint damage was not consistently demonstrated across both studies, indicative of more heterogeneous population in PSUMMIT II where less benefit was observed. As expected, patients with higher inflammatory markers (CRP) at baseline tended to show more benefit. At Week 100 based on PUMMIT I data, the progression of structural damage, in terms of total modified sharp score (for PsA), in the combined (45 mg and 90 mg both USK doses) USK group versus placebo switch group was 1.07 (SD 4.471) versus 2.26 (SD 12.578). The data is recommended for inclusion in the *Clinical Trials* section of the PI.

Advice from ACPM is requested.

13. Pending advice from the ACPM, the submitted clinical data support approval of '*Ustekinumab alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) when response to previous non-biological DMARDs has been inadequate.'*

**Summary of issues**

- Dosing regimen for PsA indication has not been systematically investigated for the new indication but is justified based on the approved dose in plaque psoriasis.
- Proposed first line use rather than second line use which is more reflective of clinical trials data.
- Validity of claim of inhibition of structural damage and its inclusion in the therapeutic indication.

**Proposed action**

The Delegate had no reason to say, at this time, that the submission, with a modified therapeutic indication, should not be approved for registration

**Request for ACPM advice**

Advice from the ACPM is requested on the following specific issues:

1. Does the committee consider extrapolation of dosing regimen approved in plaque psoriasis as adequate approach for use in Phase III trials for psoriatic arthritis?
2. Does the committee agree with the proposed use of 90 mg higher dose as 'alternative' dose in patients with body weight > 100 kg?
3. Does the committee consider restriction to second line use ('*inadequate response with non-biologic DMARDs*') appropriate reflection of the clinical trials population?
4. Does the committee consider the inclusion of advice to '*consider discontinuation of treatment in non-responders after 28 weeks of treatment'* as clinically appropriate?
5. Does the committee consider the submitted 24/52/100 week radiograph data as clinically significant and sufficiently supportive of the claim of inhibitory effect on structural damage for inclusion in the therapeutic indication?

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**

The sponsor thanks the Delegate for the opportunity to provide comment to the ACPM on the particular issues raised (see below).

The sponsor agrees with the Delegate's proposal to approve Stelara for the treatment of psoriatic arthritis (PsA)

The sponsor would like to take this opportunity to address the following comments raised in the Delegate's Request for the ACPM's Advice:

The Delegate has raised issues which we have grouped under the following headings:

1. Dosage Regimen for PsA Indication
2. Proposed First Line use Rather Than Second Line use

3. Discontinuation of Treatment in Non-responders
4. Validity of Claim of Inhibition of Structural Damage

### *1. Dosage regimen for PsA indication*

*Question 1*

*Does the committee consider extrapolation of dosing regimen approved in plaque psoriasis as an adequate approach for use in Phase III trials for psoriatic arthritis?*

*Sponsor's response*

The doses and dose regimen selected for evaluation in the Phase III CNTO1275PSA3001 and CNTO1275PSA3002 studies were based on results of the C0743T10 Phase II PsA study as well as supportive pharmacokinetic (PK) data from the dosing regimens studied in the psoriasis clinical development program. The C0743T10 study showed that a significantly greater proportion of subjects with active PsA who received 4 weekly doses of 63 mg ustekinumab at Weeks 0, 1, 2 and 3 achieved ACR 20, ACR 50, ACR 70 and PASI 75 responses at Week 12 compared with subjects randomized to placebo. Observations suggested the following:

1. that exposures achieved by the 2 or 4 dose regimen studied in C0743T10 were adequate to achieve improvements in PsA signs and symptoms, and
2. that the responses achieved by each dosing regimen were maintained for approximately 12 weeks before the response rates declined.

Based on these considerations, the CNTO1275PSA3001 and CNTO1275PSA3002 studies were designed to achieve exposures generally comparable to those studied in C0743T10 and to evaluate maintenance regimens with dosing q12w.

Since there is considerable disease overlap between psoriasis and PsA, PK analyses were conducted to examine whether it would be appropriate to leverage the dosing regimens already established for the treatment of psoriasis as dosing regimens for PsA.

The 90 mg dosing regimen studied in the psoriasis studies yielded trough serum ustekinumab concentrations that were between the concentrations approximately 12 weeks after the 2 dose regimen and the 4 dose regimen studied in C0743T10. Since the 2 dose and 4 dose regimens yielded generally similar efficacy, it could reasonably be expected that a dosing regimen that provides exposures intermediate between these regimens (that is, the 90 mg regimen studied in psoriasis) would provide similar or lower efficacy. The 45 mg dosing regimen studied in the psoriasis studies yielded trough serum ustekinumab concentrations that were consistent with or slightly lower than the serum ustekinumab concentrations achieved 12 weeks after the lower dosing regimen studied in C0743T10. It could reasonably be expected that a dosing regimen that provides exposures slightly lower than the 2 dose PsA regimen (that is, the 45 mg regimen studied in psoriasis) would provide similar or lower efficacy.

Based on these considerations, it was deemed reasonable to study the same dosing regimens in the PsA Phase III program that had been studied in the psoriasis Phase III clinical program (that is, ustekinumab 45 mg or 90 mg at Week 0 and Week 4, followed by q12w maintenance therapy). Further details on the justification for the doses studied in Phase III were provided in the sponsor's *24-Week Summary of Clinical Efficacy*.

*Question 2*

*Does the committee agree with the proposed use of 90 mg higher dose as 'alternative' dose in patients with body weight >100 kg?*

*Sponsor's response*

The sponsor acknowledges that the incremental benefit of 90 mg in patients weighing >100 kg is more consistently evident on PASI responses than for the other clinical findings in PsA. However, the totality of the clinical and PK data and the PK/PD modelling analyses support a weight-based dosing approach for ustekinumab in PsA.

Considerations leading to this conclusion include:

- In general, a higher proportion of subjects responded to 90 mg dosing compared with 45 mg dosing. There was a general consistency of incremental benefit across categorical variables at multiple thresholds (for example, ACR 20, 50, 70). Moreover, analyses of continuous variables (such as C-reactive protein) also suggested that subjects in the 90 mg group achieved an improvement, which suggests that a broader population may have incrementally benefitted. Although subject to clinical judgment, even the modest incremental benefit of 90 mg compared to that achieved in subjects treated with 45 mg may be clinically relevant for certain subjects.
- A distinct subpopulation was not readily identified that clearly accounted for the incremental benefit of 90 mg dosing but a number of considerations led to the proposal that subjects >100 kg are most appropriate for the 90 mg dose:
  - Serum ustekinumab levels were impacted by weight and PK and PK/PD analyses showed an association of serum ustekinumab concentrations to efficacy.
  - Subjects weighing >100 kg who received 90 mg dosing had similar ustekinumab exposure as subjects ≤ 100 kg treated with 45 mg.
  - Subjects with trough serum ustekinumab concentrations below the lowest quantifiable concentration had lower response rates compared to subjects with quantifiable serum concentrations. Over 50% of subjects weighing >100 kg who received ustekinumab 45 mg had trough serum ustekinumab concentrations below the lowest quantifiable
  - Concentration at Week 16, suggesting that these subjects may need a 90 mg dose to achieve quantifiable serum trough concentrations and as a result increased responses.
  - Data through Week 100, now available from Study CNTO1275PSA3001, provides the clearest evidence of the incremental benefit of 90 mg for subjects weighing >100 kg. Both the Week 52 and Week 100 data in Study CNTO1275PSA3001 continue to demonstrate that the proportion of subjects achieving ACR responses is higher in the 90 mg group than in the 45 mg group for subjects weighing >100 kg, while the response rates are comparable between subjects who received either 45 mg or 90 mg in subjects weighing ≤ 100 kg. In this study, a continued association between PK (exposure) and efficacy is observed through Weeks 52 and 88 and a similar impact of weight on PK as observed at Week 24 is also seen. However, as observed at Week 24, an ACR dose response remains unclear for subjects weighing >100 kg at Week 52 in the smaller CNTO1275PSA3002 study that enrolled a more heterogeneous population.
- Posology generally similar to psoriasis would be preferred since PsA and psoriasis commonly coexist (approximately 75% of patients with PsA have active psoriasis) and a similar dosing regimen would be potentially attractive to enable prescribers to treat both diseases simultaneously with a single treatment regimen.
- Finally, the safety profile of ustekinumab in subjects with PsA was generally consistent with that observed in subjects with psoriasis. In clinical studies in psoriasis with up to 5 years of treatment as well as in approximately 5 years of postmarketing experience,

ustekinumab has demonstrated a stable and continued favourable safety profile. Using the higher dose in patients >100 kg is thus not expected to raise any safety concerns.

In conclusion, the sponsor believes that the totality of the clinical efficacy and PK data and the PK/PD modelling analyses, together with the finding that the safety profile observed for ustekinumab in the PsA Phase III studies was similar to that observed in psoriasis. In addition, as there was no evidence of a difference in safety events based upon ustekinumab dose, the recommendation of a similar weight-based dosing approach for ustekinumab in PsA as in psoriasis is thus supported, specifically that a dose of 90 mg could be utilised in patients with body weight >100 kg.

### *1.2. Proposed first line use rather than section line use*

*Question 3*

*Does the Committee consider restriction to second line use ('inadequate response with non-biologic DMARDs') an appropriate reflection of the clinical trials population?*

*Sponsor's response*

The sponsor agrees that the label should reflect the population studied. As described in the sponsor's *24-Week PsA Clinical Overview*, the population included subjects who failed DMARDs or NSAIDs. Therefore, the proposed indication has been amended to reflect restriction to second line use following inadequate response to non-biologic DMARDs.

### *1.3. Discontinuation of treatment in non-responders*

*Question 4*

*Does the Committee consider the inclusion of advice to 'consider discontinuation of treatment in non-responders after 28 weeks of treatment' as clinically appropriate?*

*Sponsor's response*

The sponsor agrees it is clinically appropriate to include the advice to '*consider discontinuation of treatment in nonresponders after 28 weeks of treatment*'. This advice is included in the Stelara EU SmPC as well as the Australian PI for psoriasis. Therefore, the *Dosage and Administration* section of the PI has been amended to include this information.

### *1.4. Validity of claim of inhibition of structural damage*

*Question 5*

*Does the Committee consider the submitted 24/52/100 week radiographic data as clinically significant and sufficiently supportive of the claim of inhibitory effect on structural damage for inclusion in the therapeutic indication?*

*Sponsor's response*

The sponsor prefers to support the inclusion of '*inhibition of structural damage'* in the indication and awaits consideration of this by the ACPM.

### *2. Comments on risk management plan and ASA*

*RMP evaluator's comment 1*

*It was drawn to the Delegate's attention that the approved indications in the EU position Stelara as a second line therapy for the treatment of active psoriatic arthritis in adults rather than as first line therapy as sought for in Australia. Consequently the sponsor was asked to explain the reasons for this difference in indications between the EU and Australia in a revised ASA, as per the Risk Management Plan (RMP) Questions & Answers (Version 1.3, October 2012) on the TGA website. The sponsor has provided justification for these differences maintaining that ustekinumab was shown to be effective in both subjects who were exposed to previous DMARD therapy and those who were not exposed to previous*

*DMARD therapy in the Phase III clinical studies. However, such information was not included in the updated ASA. The Post-Market Surveillance Branch will be guided by the clinical evaluator and Delegate's assessment of the acceptability of the sponsor's justification. Nevertheless it is reiterated that the sponsor should identify and explain the reasons for the difference in indications between the EU and Australia in a revised ASA before this application is approved.*

*Sponsor's response*

The sponsor has agreed to amend the indication wording to align with that approved in the EU, subject to consideration by the ACPM, as follows:

> *Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) when response to previous non-biological DMARDs has been inadequate.*

Consequently, the ASA does not require updating.

*RMP evaluator's comment 2*

*The sponsor was asked to provide a table summarising the pharmacovigilance plan and risk minimisation plan proposed for Australia in the ASA. It was suggested that wording pertaining to all the specified ongoing safety concerns in the proposed Australian PI and CMI should be included in the table. The sponsor states: 'The Stelara ASA has been amended to incorporate the recommendation (Stelara ASA, Section 6).' However, Section 6 of the updated ASA only details risk minimisation activities and is not inclusive of pharmacovigilance activities. It is recommended that the sponsor maintain this section of the ASA and also include a table summarising the pharmacovigilance and risk minimisation activities for all of the specified ongoing safety concerns and missing information proposed for Australia in a revised ASA, which should be submitted for review before this application is approved.*

*Sponsor's response*

The sponsor agrees to update the ASA to maintain the pharmacovigilance activity section of the ASA, and also agrees to include a table summarising the pharmacovigilance and risk minimisation activities.

*RMP evaluator's comment 3*

*Section 6: 'Summary Table of Risk Minimisation Measures for Australia' of the updated ASA indicates that there are no proposed routine risk minimisation measures for the important identified risk: 'Facial palsy'. It is recommended to the Delegate that the Adverse Effects section of the proposed Australian PI be amended to include 'Facial palsy' as an uncommon ADR, similar to the current EU SmPC, to enhance safe use of these medicines.*

*Sponsor's response*

The sponsor has previously provided the rationale for not including 'Facial palsy' as an uncommon adverse drug reaction (ADR) in response to TGA's Clinical Evaluation Report dated 13 September 2013 for the 5-year psoriasis submission. Key factors supporting this conclusion included a small number of cases and the absence of un-confounded cases reporting a positive rechallenge. Based on the evaluation of the data, the sponsor did not consider facial palsy to be reasonably causally related to treatment with ustekinumab and therefore not an ADR. The response was accepted by the TGA. Information to date has not changed the sponsor's causality assessment.

*RMP evaluator's comment 4*

*For the important potential risk: 'Exposure during pregnancy', it was noted the currently approved UK SmPC was more restrictive than the currently approved Australian PI. The Delegate was requested to consider including these more restrictive statements in the proposed Australian PI to enhance safe use of these medicines. The sponsor states:*

*Regarding point 2, Janssen received the same question from TGA with the evaluation of the ustekinumab psoriasis 5-year data. In response to the question submitted at that time, the TGA accepted the rationale not to include these more restrictive warnings. Since the response submitted to TGA, Janssen has not identified any new safety concerns in pregnancy that might warrant us to reconsider the position.*

*The Post-Market Surveillance Branch will be guided by the clinical evaluator and Delegate's assessment of the acceptability of the sponsor's justification.*

*Sponsor's response*

The sponsor maintains that they have not identified any new safety concerns in pregnancy that might warrant us to reconsider the position.

### *Sponsor's conclusion*

In summary, the sponsor believes that Stelara has a favourable benefit: risk profile and is considered effective in the treatment of PsA. The sponsor agrees with the Delegate's recommendation to approve the extension of indications for Stelara to include PsA. The sponsor proposes that the indication wording be approved as follows:

> *Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) when response to previous non-biological DMARDs has been inadequate.*

However, as the sponsor would prefer to support the inclusion of '*inhibition of structural damage*' in the indication, the sponsor awaits consideration of this by the ACPM.

## Advisory Committee Considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Stelara solution for injection containing 45 mg in 0.5 mL and 90 mg in 1 mL of ustekinumab to have an overall positive benefit–risk profile for the Delegate's amended indication**;**

> *Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years or older) where response to previous non-biological DMARD therapy has been inadequate.*

In making this recommendation the ACPM considered that the claim regarding structural damage is more appropriate in the *Clinical Trials* section of the PI.

## Proposed conditions of registration

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

## Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Remove the weight based dosing and replace with a statement that some patients received 90 mg in clinical trials and derived a benefit.
- Include the results of effect on structural joint damage under *Clinical Trials*.

- Include the statement from the EU SmPC regarding the use of contraception in the PI as it contains specific advice about how long contraception should be continued after treatment with ustekinumab*: Women of childbearing potential: should use effective methods of contraception during treatment and for at least 15 weeks after treatment.* A suitable statement on the issue should be added to the CMI.

**Specific advice**

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

1. Does the committee consider extrapolation of dosing regimen approved in plaque psoriasis as adequate approach for use in Phase III trials for psoriatic arthritis?

The ACPM advised that the extrapolation of dosing regimen approved in plaque psoriasis for use in Phase III trials for psoriatic arthritis was reasonable and was similar to the approach used for the tumour necrosis factor (TNF) inhibitors.

2. Does the committee agree with the proposed use of 90 mg higher dose as 'alternative' dose in patients with body weight > 100 kg?

The ACPM noted that the pivotal trials were not designed to assess weight based dosing. There is little evidence from the total population that there is consistent additional benefit of a higher dose. The ACPM agreed that some patients did benefit from an increased dose; however, patients weighing more than 100 kg should not necessarily be initiated on the higher dose as there was limited evidence of an incremental benefit, unlike when used in the treatment of psoriasis where an incremental benefit was seen. The ACPM considered that the 90 mg dose should not be limited to patients 100 kg or more and that the PI should state that some patients received 90 mg in clinical trials and derived a benefit, rather than specifying or implying that the 90 mg dose should be used in patients weighing 100 kg or more.

3. Does the committee consider restriction to second line use ('inadequate response with non-biologic DMARDs') appropriate reflection of the clinical trials population?

The ACPM noted that the sponsor has agreed to a second line indication and considered this to be appropriate based on the data from the clinical trials.

4. Does the committee consider the inclusion of advice to 'consider discontinuation of treatment in non-responders after 28 weeks of treatment' as clinically appropriate?

The ACPM considered that it is appropriate that non-responders should discontinue treatment at 28 weeks. The ACPM noted that the sponsor, in its pre-ACPM advice, acknowledged that this advice is included in the Stelara EU SmPC as well as the Australian PI for psoriasis. The sponsor agreed to amend the *Dosage and Administration* section of the PI to include this information.

5. Does the committee consider the submitted 24/52/100 week radiograph data as clinically significant and sufficiently supportive of the claim of inhibitory effect on structural damage for inclusion in the therapeutic indication?

The ACPM considered that the data are not particularly robust. The committee noted that with the availability of biological disease modifying agents and early treatment of patients, the use of changes in modified Sharpe score had become an insensitive indicator and a more sensitive validated indicator was required. The ACPM noted the sponsor in its pre-ACPM response indicated that it preferred that the statement remain in the indication. However, the ACPM agreed with the Delegate's approach that statement should be removed from the indication and the relevant results be included in the *Clinical Trials* section of the PI.

The ACPM 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 Stelara containing 45 mg/0.5 mL and 90 mg/1.0 mL ustekinumab solution for injection for the new indication:

> *Psoriatic Arthritis (PsA)*
> *Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) where response to previous non-biological DMARD therapy has been inadequate.*

### Specific conditions of registration applying to these goods

Only include those unique to this product (for most applications this is only the first paragraph on implementing the RMP.

1. The ustekinumab European Risk Management Plan (EU-RMP), version 11.0, dated 24 September 2013 with an Australian Specific Annex (Version: 2.4, dated 21 January 2015), included with submission PM-2013-04148-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

# Attachment 1. Product Information

The Product Information approved for Stelara at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

# Attachment 2. Extract from the Clinical Evaluation Report

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