Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sarilumab (rch)

Proprietary Product Name: Kevzara, Ilsidex

Sponsor: Sanofi-Aventis Australia Pty Ltd

June 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee for Medicines
ACPM	Advisory Committee for Prescription Medicines
ACR	American College of Rheumatology
ACSOM	Advisory Committee for the Safety of Medicines
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell mediated cytotoxicity
AIA	Antigen induced arthritis
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BMI	Body mass index
CCP	Cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CDC	Complement dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CIA	Collagen induced arthritis
C_{max}	Maximum serum drug concentration
CPD	Certified Product Details
CRP	C-Reactive Protein
CS	Corticosteroids
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Meaning
C_{trough}	Trough concentration
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 isozyme 3A4
DAS28	Disease Activity Score 28
DMARD	Disease modifying anti-rheumatic drug
ECG	Electrocardiography
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation ratio
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
gp130	Glycoprotein 130
GMP	Good Manufacturing Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
hERG	Human ether-à-go-go-related gene
HLGT	High-Level Group Term
IFN	Interferon
IL	Interleukin
IL-6	Interleukin 6
IL-6R	Interleukin 6 receptor
IMP	Investigational medicinal product
ITT	Intention-to-treat
IV	Intravenous(ly)
JAK/STAT	Janus kinase/signal transducer and activator of transcription
KD	Dissociation constant
KLH	Keyhole limpet haemocyanin (a T cell-dependent antigen)
LIF	Leukaemia inhibitory factor

Abbreviation	Meaning
MACE	Major adverse cardiac events
MAPK	Mitogen activated protein kinase
MCR	Major Clinical Response
mIL-6R	Membrane bound interleukin 6 receptor
mIL-6Rα	Membrane bound interleukin 6 receptor (alpha subunit)
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NMSC	Non-melanoma skin cancer
NNH	Number needed to harm
NNT	Number needed to treat
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic
PFS	Pre-filled syringe
PK	Pharmacokinetic
PY	Patient years
QOL	Quality of life
qw	Once a week (dosing interval)
q2w	Once every 2 weeks (dosing interval)
RA	Rheumatoid arthritis
REGN844	A surrogate murine monoclonal antibody against mouse IL-6Rα
RF	Rheumatoid factor
RMP	Risk management plan
SAA	Serum amyloid A
SAE	Serious adverse event
SAR	Sarilumab

Abbreviation	Meaning
SC	Subcutaneous(ly)
SDAI	Simplified Disease Activity Index
SD	Standard deviation
sIL-6R	Soluble IL-6 receptor
sIL-6Rα	Soluble interleukin 6 receptor (alpha subunit)
SmPC	Summary of product characteristics
SOC	System Organ Class
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
TLR4	Toll-like receptor 4
TNF	Tumour necrosis factor
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
WT	Wild type

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Withdrawn 26 April 2017
Date of decision:	Not applicable
Date of entry onto ARTG:	Not applicable
Active ingredient:	Sarilumab (rch)
Product names:	Kevzara, Ilsidex
Sponsor's name and address:	Sanofi-Aventis Australia Pty Ltd Locked bag 2227 North Ryde BC NSW 1670
Dose form:	Solution for injection
Strengths:	150 mg and 200 mg
Container:	Pre-filled syringe
Pack sizes:	Not applicable
Approved therapeutic use:	Not applicable
Route of administration:	Subcutaneous
Dosage:	Not applicable
ARTG numbers:	Not applicable

Product background

This AusPAR describes the application by Sanofi-Aventis Australia Pty Ltd (the sponsor) to register Kevzara sarilumab (rch) solution for subcutaneous (SC) injection for the following indication:

> *'Kevzara in combination with non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) is indicated for the treatment of moderate to severe Rheumatoid Arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs'.*

The sponsor also included in the submission the application for an additional trade name Ilsidex.

Sarilumab (rch) is a human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin 6 receptors (IL-6R), (sIL-6R and mIL-6R), and has been shown to inhibit interleukin 6 (IL-6) mediated signalling through these

receptors. It is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony erosion and ultimately loss of function of the affected joints The over-production of pro-inflammatory cytokines such as tumour necrosis factor (TNF) and IL-6 in the joints and sera of patients with rheumatoid arthritis are important mediators in the disease pathogenesis primarily via activation of T lymphocytes, but also through effects on B lymphocytes. IL-6 can activate hepatocytes to produce acute phase reactants, such as C reactive protein (CRP). The mode of action of sarilumab is by the inhibition of signalling mediated by both soluble and membrane-bound IL-6 receptors.

The proposed dose of sarilumab is 200 mg, once every 2 weeks (q2w), given by SC injection. It is recommended that the dose of sarilumab be reduced from 200 mg every fortnight to 150 mg q2w for the management of neutropaenia, thrombocytopaenia or elevated liver enzyme tests.

Regulatory status

At the time the TGA considered this application, similar applications had been approved, rejected or were under consideration in the (country date) as shown in Table 1.

Country	Submission date	Status
EU	July 2016	pending
USA	30 October 2015	pending
Canada	28 January 2016	Approved 12 January 2017
Switzerland	Not applicable	Not applicable
New Zealand	Not applicable	Not applicable

II. Registration time line

Table 2: Registration timeline for submission PM-2015-04024-1-3

Description	Date
Submission dossier accepted and 1st round evaluation commenced	29 January 2016
First round evaluation completed	8 July 2016
Sponsor provides responses on questions raised in the first round evaluation	12 September 2016
Second round evaluation completed	14 October 2016
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	1 November 2016

Description	Date
Sponsor's pre-Advisory Committee meeting response	15 November 2016
Advisory Committee meeting	1 - 2 December 2016
Sponsor provides additional safety data	31 January 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	14 March 2017
Sponsor's pre-Advisory Committee meeting response	28 March 2017
Advisory Committee meeting	6 - 7 April 2017
Submission withdrawal	26 April 2017
Number of TGA working days from submission dossier acceptance to submission withdrawal	198

III. Quality findings

Drug substance (active ingredient)

Sarilumab (rch)(IgG1 isotype monoclonal antibody) is a covalent heterotetramer consisting of 2 disulphide linked human heavy chains, each covalently linked through a disulphide bond to a human kappa light chain. There is a single N-linked glycosylation site (Asn296) on each heavy chain, located within the CH_2 domain of the Fc constant region in the molecule.

Figure 1: Diagrammatic representation of the structure of sarilumab

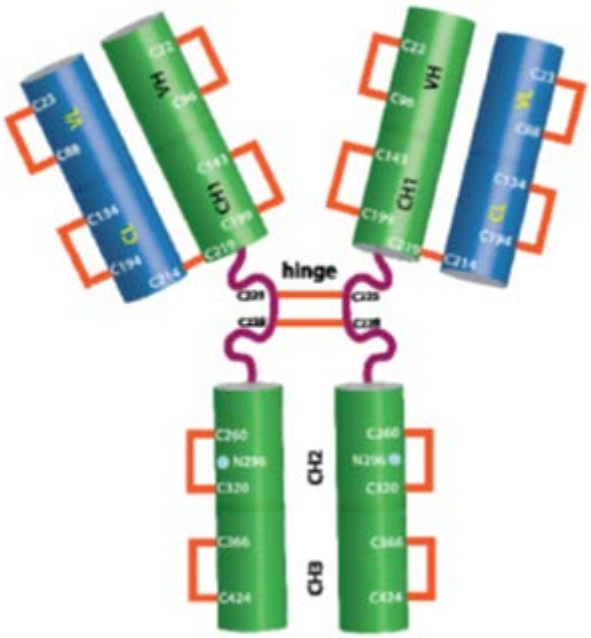


Figure description: Representation of the structure of sarilumab depicting the location of each of the intrachain and interchain disulphide bonds (orange). Heavy (green) and light (blue) chains are connected by interchain disulphide bonds; heavy chain dimerisation is achieved through 2 heavy chain intermolecular disulphide bonds located within the hinge region. The Fc domain glycosylation site is also indicated (cyan).

Sarilumab specifically binds to the membrane-bound and soluble forms of the IL-6R alpha subunit (mIL-6Rα and sIL-6Rα) and inhibits IL-6 mediated signalling. It has an average molecular weight of 149.6 kDa, with 2 N-linked glycosylation sites (1 glycosylation site per heavy chain (Asn^{296}).

Sarilumab is produced in CHO cell suspension culture. The product is purified from the bioreactor using affinity chromatography, followed by virus inactivation and further chromatographic, concentration and purification steps before formulation.

Drug product

The manufacturing process for production of bulk prefilled syringes consists on the following steps:

- Step I: Thawing of sarilumab 131.6 mg/mL or 175 mg/mL formulated drug substance.
- Step II: Pooling of sarilumab 131.6 mg/mL or 175 mg/mL formulated drug substance.
- Step III: Pre-filtration of formulated bulk drug substance.
- Step IV: In-line sterilising filtration, aseptic filling of bulk drug product solution into syringe, and stoppering.
- Step V: 100% visual inspection of bulk prefilled syringes.

Further manufacturing steps for the prefilled syringes are assembly with plunger rod and finger flange. All manufacturing steps are validated.

The TGA was still reviewing the submission for Good Manufacturing Practice (GMP) clearances at the time the quality Advisory Committee For Prescription Medicines (ACPM) summary was written.[1]

Specifications were provided for the drug substance and drug product. All analytical procuress used were validated.

Stability data have been generated under real time and stressed conditions. Photostability data indicated that the product is not photostable. In-use stability data have also been submitted.

Approved shelf life (include temperature excursion during shipping if necessary) 24 months storage at 2 to 8°C; protected from light. Use the syringe within 14 days after taking it out of the refrigerator or insulated bag (when stored at room temperature).

Quality summary and conclusions

There are no objections on quality grounds to the approval of Kevzara/Ilsidex.

The TGA is still reviewing the GMP clearances at 5 sites.

The company is required to provide evidence of valid GMP clearances prior to product registration.

[1] The name of the committee changed during the time of this submission, the initial presentation was to Advisory Committee for Prescription Medicines (ACPM) at Meeting 313 and the second presentation was to the Meeting 2 of the Advisory Committee for Medicines (ACM).

Proposed conditions of registration

Batch Release Testing and Compliance with Certified Product Details (CPD):

1. It is a condition of registration that all batches of Kevzara/Ilsidex imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Kevzara/Ilsidex imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

IV. Nonclinical findings

Introduction

Interleukin-6 (IL-6) is a multifunctional cytokine which is produced by a variety of cell types, and is involved in the pathogenesis of neoplasia, osteoporosis and various inflammatory diseases, including rheumatoid arthritis as well as inflammatory bowel disease. Elevated tissue and serum levels of IL-6 have been noted in the disease pathology of rheumatoid arthritis, thus the inhibition of the biological activity of IL-6 or its receptor can potentially be utilised in the treatment of the disease.

The proposed dosing regimen involves SC administration of a solution in a prefilled syringe (PFS) delivering either a 150 mg (131.6 mg/mL) or 200 mg (175 mg/mL) dose. The recommended dose of sarilumab is 200 mg q2w, with an option to reduce the dose to 150 mg q2w to manage patients who may experience decreased neutrophil counts, decreased platelet counts or elevated liver transaminases.

Overall quality of the nonclinical dossier

The dossier of pharmacology studies consisted of original studies, and covered the mechanism of action as well as in vitro and in vivo efficacy in a murine joint inflammation model. Sarilumab does not bind to mouse IL-6Rα, and therefore a surrogate murine monoclonal antibody against mouse IL-6Rα (REGN844) was generated to conduct pharmacology and reproductive and developmental toxicology studies in wild type (WT) mice.

A murine in vivo pharmacology study with sarilumab was performed in double humanised (IL-6hu/hu IL-6Rαhu/hu) mice expressing human IL-6 and the human ectodomain of IL 6Rα instead of the equivalent mouse gene products. All toxicology studies were performed in responsive species, either in monkeys (using sarilumab) or mice (using REGN844). The studies were Good Laboratory Practice (GLP) compliant and generally appeared to be concordant with relevant guidelines (ICH S6).[2] The dossier was of adequate quality to enable an assessment of the toxicity of the proposed product to be conducted. In addition, the sponsor provided a number of studies published in the literature describing the role of IL-6/IL-6R in normal cellular processes and in rheumatoid arthritis.

All of the original sarilumab toxicology studies were conducted with the same formulation buffer and original manufacturing process (P1) used in the Phase I clinical trials. A new

[2] ICH S6 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals S6(R1).

process (P3, used in Phase III clinical trials) was only used in a bridging study in monkeys (in which no toxicological differences were observed between process formulations P1 and P3).

Pharmacology

Primary pharmacology

Dysregulation of IL-6-type cytokine signalling contributes to the onset and maintenance of several diseases, including rheumatoid arthritis, and in fact IL-6 is found in rheumatoid arthritis synovial tissue. The key studies submitted with this application focussed on the ability of sarilumab (and its murine surrogate) to block the interaction of IL-6Rα with IL-6 (and therefore to block IL-6 induced receptor signalling). Three in vivo pharmacology studies were submitted, one using sarilumab in a double humanised mouse (IL-6hu/huIL-6a hu/hu), and two using REGN844 in WT mice.

IL-6 exerts its action through interaction with either a membrane bound or soluble form of the IL-6 receptor (mIL-6R and sIL-6R, respectively). The sarilumab dissociation constant (KD) for human and monkey IL-6Rα was 54 and 123 pM respectively whereas the dissociation constant of REGN844 for mouse IL-6Rα was 193 pM.

Sarilumab bound to monkey and human PBMCs, and not to PBMCs of dogs, sheep, mini-pigs, rabbits, hamsters, guinea pigs, rats or mice. Sarilumab also bound to human and monkey tissues with a very similar pattern of immunohistochemistry staining. Specific staining was almost exclusively detected in the cytoplasm and/or cytoplasmic granules in tissues of both species. Membrane staining was not observed in any of the human tissues and only in mammary gland epithelium from one monkey. The potential toxicological impact of the cytoplasmic binding is unknown, but of little concern since access to the antibody by the cytoplasm in vivo is not expected. Taken together, the monkey was an appropriate species for the evaluation of the pharmacology, pharmacokinetics and toxicology of sarilumab.

IL-6 is a cytokine from a family of mediators which modulate the immune response, including induction of inflammation, and are involved in the regulation of the acute phase response to injury and infection. It is produced by T cells, monocytes and fibroblasts and induces B cell and T cell proliferation and differentiation, as well as the differentiation of macrophages, osteoclasts, and megakaryocytes. As anticipated from these functions, IL-6 also has a role in haematopoiesis, but is also implicated in liver and neuronal regeneration, embryonic development and fertility. A pleiotropic effect of IL-6 is to be anticipated, since the signal transducer in both cases is the glycoprotein 130 protein (gp130), the interaction resulting in the activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) and mitogen activated protein kinase (MAPK) cascades.

Sarilumab blocked IL-6 dependent STAT-3 activation in HepG2 human hepatocarcinoma cells (expressing membrane-bound IL-6Rα), and trans-signalling (induced by a combination of IL-6 and soluble IL-6Rα) in an engineered HEK-293 cell line over expressing gp130 but not expressing IL-6Rα. In vitro cell-based assays for antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) did not detect Fc effector function activity associated with sarilumab.

The mouse surrogate IL-6Rα antibody, REGN844, bound mouse IL-6Rα (KD 193 pM) with a similar potency to that of sarilumab with human and monkey receptors (54 and 123 pM). REGN844 inhibited the binding of human IL-6 to mouse IL-6Rα (IC50: 4 nM) and the (IL-6 induced) proliferation of a mouse B cell hybridoma cell line (IC50: 110 pM).

Turpentine induced elevation of serum amyloid A (SAA) (an inflammation biomarker) was inhibited by sarilumab in double humanised (IL-6hu/huIL-6Rαhu/hu) male mice

expressing human IL-6 and the ectodomain of human IL-6Rα, and by REGN844 in WT mice. In these studies, there was a trend towards increased concentrations of circulating IL-6 (human or mouse), supporting the argument that circulating IL-6 cannot bind the receptors since they are blocked by the antibody.

In the collagen induced arthritis murine model, in which collagen was administered to cause autoimmunity to collagen and inflammation of synovial joints, prophylactic administration of REGN844 (10 or 30 mg/kg twice weekly) mitigated inflammation and bone erosion.

Taken together, the results from the nonclinical studies described above support the proposed mechanism of action (direct inhibition of the binding between IL-6 and IL-6Rα) and the proposed indication.

In mice, the serum IL-6 level was higher in the presence of the murine anti-IL-6R antibody (REGN844 in this submission, and MR16-1 in Mihara et al., 2002).[3] Intravenous (IV) administration of sarilumab increased serum IL-6 levels in monkeys (26 week IV study). The most likely explanation is the displacement of IL-6 from the receptor, but a feedback-mediated change in its synthesis or elimination in the presence of an anti-IL-6R antibody such as sarilumab may also be possible.

The rapid turnover rate of the IL-6R (half-life of 2 to 3 hours) combined with continuous production of IL-6 during chronic inflammation suggests that a continuous presence of sarilumab is required for effective receptor inhibition. The need for continuous sarilumab presence was not evaluated due to the lack of a study using monkeys experiencing inflammation.

Sarilumab suppressed the IL-6/sIL-6R-induced STAT3 activation in human gp130 overexpressing HEK293 cells, indicating that sarilumab/sIL-6R complexes are not biologically active. Dissociation of IL-6 and sIL-6R from their preformed complex in vitro due to sarilumab, and the effect of sarilumab on the levels or function of other interleukins, were not investigated.

There was evidence in the published literature to suggest that IL-6 is involved in the pathology of rheumatoid arthritis. Firstly, as reviewed by Wong et al., (2003);[4] IL-6-/- mice are protected against joint inflammation and destruction in both collagen induced arthritis (CIA) and antigen induced arthritis (AIA). While complete protection (no arthritis) was seen in one CIA study;[5] amelioration (reduced severity and/or delayed onset) of arthritis was seen in other studies (with both CIA and AIA). This protection was seen despite the expression of both TNF and Interleukin 1 (IL-1) in the inflamed synovium, indicating a particularly important role for IL-6 in these models of disease. In one study, arthritis was reduced and failed to progress to a chronic infiltrate in both AIA and zymogen induced arthritis models in IL-6-/- mice.[6] These findings suggest that IL-6 is important in either maintaining acute inflammation or converting it into a chronic phase. Secondly, (as also noted in Wong et al., 2003); an IL-6R neutralising antibody suppressed the onset and reduced the severity of CIA in mice. However, complete suppression of arthritis occurred only when the blocking antibody was administered on Days 0 or 3, indicating that IL-6 is important in the early phase of disease.

[3] Mihara M, et al (2002). Influences of anti-mouse interleukin-6 receptor antibody on immune responses in mice. *Immunol Lett*. 2002; 84:223-229.
[4] Wong P et al. The role of the interleukin-6 family of cytokines in inflammatory arthritis and bone turnover. *Arthritis Rheum*. 2003; 48: 1177-1189
[5] Alonzi T et al. Interleukin 6 is required for the development of collagen-induced arthritis. *J Exp Med*. 1998; 187: 461-468
[6] De Hooge A et al. Involvement of Il-6, apart from its role in immunity, in mediating a chronic response during experimental arthritis. *Am J Pathol*. 2000; 157: 2081-2091

The only model of arthritis/inflammation investigated in this submission was in mice, which received the surrogate antibody REGN844. Therefore radiological and histopathological evidence of the therapeutic effect of sarilumab per se is missing in a responsive species.

Pharmacokinetics

The pharmacokinetic (PK) profile of sarilumab was assessed following single IV and SC administration of sarilumab to rats and monkeys, and measuring free (rats) or total (monkeys) sarilumab in serum. Toxicokinetic parameters were determined in the general and reproductive, IV and SC toxicology studies in monkeys with sarilumab and in the mice with REGN844. In addition, anti-sarilumab antibodies were also determined in the toxicology studies to assess the impact of anti-sarilumab antibodies on sarilumab exposure and to evaluate any toxicity associated with formation of anti-sarilumab antibodies. Conventional metabolism studies were not conducted with sarilumab, and were not required. Plasma protein binding was not evaluated, which is acceptable as sarilumab would not be expected to bind to plasma proteins. IgG molecules do not cross the blood-brain barrier. Standard distribution, metabolism and excretion studies were not conducted and are not required for an antibody. The pharmacological activity of the drug in the species chosen for toxicity testing is the critical factor in the choice of species as the metabolic pathways for antibodies are generally understood and are consistent between species.

Bioavailability after SC dosing was approximately 78% in monkeys after single dosing. The low volume of distribution suggested that sarilumab was largely confined to the vascular compartment, with limited extracellular fluid distribution. There was no evidence, in either rabbits or cynomolgus monkeys, of a sex difference in the PK of REGN844 or sarilumab, respectively.

Sarilumab crossed the placenta and/or was excreted in milk in monkeys, since infants from mothers which received sarilumab up to parturition, had measurable levels of sarilumab up to Day 30 of birth. Sarilumab is expected to be excreted into milk since it has been established (in rodents) that IgG is excreted in milk and transferred to the suckling offspring via the FcRn receptor in the small intestine (for example Israel et al, 1997).[7]

Sarilumab in rats showed linear PK, which is expected of a species not expressing the target receptor.

Sarilumab exposure was continuous during repeated weekly dosing with sarilumab in most of the monkeys treated. At doses of less than 5 mg/kg/week, continuous exposure to sarilumab was not observed, likely due to the production of anti-sarilumab antibodies. In monkeys, sarilumab exposure increased dose-proportionally between 5 and 100 mg/kg/week, and accumulation was observed. Sarilumab half-life was long in monkeys and humans.

Development of anti-sarilumab antibodies was observed in most monkeys receiving 0.5 to 2 mg/kg/week, whereas minimal anti-sarilumab antibodies development was observed in animals receiving ≥ 15 mg/kg/week. The presence of anti-sarilumab antibodies responses was not unexpected due to the foreign (human) nature of the antibody to monkeys, however the draft PI document (dated 6 January 2016) states that 9.2% of patients treated with Kevzara monotherapy exhibited an anti-sarilumab antibody response, with 6.9% of patients also exhibiting neutralising antibodies.

[7] Israel E et al. Expression of the neonatal Fc receptor, FcRn, on human intestinal epithelial cells. *Immunology*. 1997; 92: 69-74

Sarilumab concentrations at higher doses were more than dose proportional, and anti sarilumab antibodies were not observed at the end of the recovery period, when sarilumab concentrations had reached low levels. Therefore the lack of an anti-sarilumab antibody response at doses ≥ 15 mg/kg/week may reflect the potential for the high circulating drug concentrations to interfere in the anti-sarilumab antibodies assay, or may indicate that high circulating sarilumab concentrations have caused immune tolerance. No toxicities related to anti-sarilumab antibodies were observed.

In humans (rheumatoid arthritis patients), the population PK of sarilumab (maximum serum drug concentration (C_{max}), area under the concentration time curve (AUC) and trough concentration (C_{trough})) were more than dose proportional, and accumulation was observed, due to the drug's nonlinear clearance and long half-life.

The potential differences in exposure between different sarilumab lots derived from different formulations and manufacturing processes were assessed in a study in monkeys of 13 weeks duration. No significant differences were observed in the different lots used (the formulation used in most nonclinical toxicological studies was also used in Phase I clinical trials, whereas the second formulation was used only in the comparative study but had been used in Phase III clinical trials). There were no nonclinical studies with sarilumab in combination with other drugs (such as methotrexate (MTX)) to support its clinical use with other drugs.

Overall, the PK profiles in the laboratory animal species used in the pivotal repeat dose toxicity studies (monkeys) were sufficiently similar to allow them to serve as appropriate models for the assessment of the drug's toxicity in humans.

Pharmacokinetic drug interactions

No nonclinical drug interactions studies were conducted. The proposed PI does state that 'Kevzara has not been investigated in combination with JAK inhibitors or biological disease modifying anti-rheumatic drugs (DMARDs)'. Clinical PK studies must be evaluated since this drug is indicated to be used concomitantly with other drugs.

Toxicology

Acute toxicity

No studies were submitted, and this is acceptable since acute toxic effects could have been ascertained from the repeat dose studies. In those studies, the maximum non-lethal dose was the maximum dose administered SC for 13 weeks, that is, 100 mg/kg/week. No mortality was observed following IV administration of sarilumab for 26 weeks at 50 mg/kg/week.

Repeat-dose toxicity

Toxicology studies were all conducted in accordance with International Conference on Harmonisation (ICH) guidelines, and included repeat dose studies of up to 6 months duration in cynomolgus monkeys, an embryofetal development study in mice (using REGN844), and a pre/post-natal study in cynomolgus monkeys. The formulations in the toxicology studies used excipients similar to those used in the clinical trials. The SC and IV routes of administration were used in the nonclinical studies to support the proposed route of administration of sarilumab to patients (SC).

In mice, REGN844 was used to study the effects of IL-6Rα inhibition in reproductive and developmental toxicology studies, in a fertility study, and in juvenile toxicology studies. The REGN844 chosen for the mouse toxicology study (200 mg/kg/week) was significantly

higher than the dose (5 mg/kg) which reduced Turpentine induced inflammation in this species. Continuous exposure to REGN844 was observed in mice in the 4 week studies.

Justification of the use of the cynomolgus monkey as the main species for the nonclinical safety evaluation of sarilumab is discussed under 'Pharmacology'. The clinical (SC) route was used in some of the toxicology studies. The weekly dosing frequency used with the cynomolgus monkey was greater than that proposed for humans (2 weekly), and since the half-life was comparable in cynomolgus monkeys and in humans, this dosing regimen adequately mimicked or exaggerated conditions under which sarilumab is proposed to be used in humans (accumulation was also observed at the higher doses). While the duration of human treatment with sarilumab has not been specified, 6 month studies in monkeys are usually acceptable for toxicity tests of a biotechnology-derived pharmaceutical for chronic indications. The mouse study with REGN844 was of 4 weeks duration, but given the length of the pivotal monkey study, and the fact that the substance used in the mice was not sarilumab, this was acceptable.

Relative exposure

Doses of sarilumab administered in the repeated-dose toxicity studies ranged from 1 to 50 mg/kg/week IV for up to 26 weeks, and 2 to 100 mg/kg/week SC for 13 weeks. Toxicokinetic data in the SC study were restricted to C_{trough} and mean serum concentration values. As anti-sarilumab antibody formation only occurred at lower doses the AUC data in Table 3 (see below) is considered valid. Although the AUC data were tabulated for comparison purposes, the dose ratios (based on mg/kg/week) are a better indicator of the relative exposure, because molecules as large as sarilumab are likely to be confined to the vasculature.

In cynomolgus monkeys, Day 1 levels were not maintained for the full duration of the study in a number of animals at the low dose (LD) and middle dose (MD), but at the high dose (HD), serum concentrations were maintained throughout the study in all animals as no animal developed anti-sarilumab antibodies, and AUC values were higher on the last sampling day than on Day 1. Therefore, the AUC values from the last sampling period (representing an adequate level of exposure to sarilumab) were used. Exposure to sarilumab was maintained in an adequate number of antibody-negative animals to sufficiently characterise its toxicity.

In summary, the doses administered in the toxicology studies exceed those in the clinical trials and provided substantially higher exposures relative to those achieved clinically. Estimated exposure levels in monkeys during the toxicity studies and a comparison to expected human sarilumab exposure are tabulated below (Table 3).

Table 3: Relative exposure in repeat dose toxicity studies in monkeys

Study, duration and route	Dose (mg/kg/week)	$AUC_{0\text{-}168h}$ (µg.h/mL)	AUC for 2 weeks (µg.h/mL)	Exposure ratio# (over 2 weeks)	
				Based on AUC	Based on dose
REGN88-TX-06040 (5 weeks) IV	5	16800	33600	3.5	2.5
	10	28050	56100	5.9	5
	40	159500	319000	33.6	20
REGN88-TX-06037 (13 weeks) IV	1	389	778	0.1	0.5
	10	61550	123100	13.0	5
	50	258313	516626	54.5	25
REGN88-TX-08031 (26 weeks) IV	0.5	186	372	0.04	0.3
	5	22892	45784	4.8	2.5
	15	90371	180742	19.1	7.5
	50	381040	762080	80.4	25
REGN88-TX-08030 (145 days; pre-post natal) IV	5	37260	74520	7.9	2.5
	15	124845	249690	26.3	7.5
	50	396455	792910	83.6	25
REGN88-TX-06038 (13 weeks) SC	2	ND	-	-	1
	10	ND	-	-	5
	30	ND	-	-	15
	100	ND	-	-	50
POH0428; (population PK) Rheumatoid arthritis patients	2[a]	-	9480[b]	-	-

= animal:human; a: 200 mg q2w to a 50-kg patient; b: AUC0–14 days of 395 mg.day/L was multiplied by 24 to convert to µg.h/mL; ND: not determined; - : not applicable.

Anti-sarilumab antibodies were induced in a number of studies, particularly at doses of ≤ 15 mg/kg/week, and resulted in a reduction in exposure to sarilumab in some animals. However, exposure to sarilumab was maintained in an adequate number of negative animals to sufficiently characterise its toxicity.

Major toxicities

There was no indication from the repeat dose toxicity studies of any target organ toxicity. The only effects observed were due to the pharmacological activity of sarilumab (IL-6Rα inhibitor).

Sarilumab caused moderate and (at least partially) reversible decreases in serum fibrinogen and serum CRP levels. Apart from the effects on fibrinogen, sarilumab did not cause any other effects on haemostasis (platelet counts, prothrombin time, activated partial thromboplastin time (APTT)).

Although IL-6R is expressed on early myeloid progenitors, stem cells and bone marrow stroma cells, the only effect observed in monkeys was neutropaenia and lower primary and secondary IgG responses following an antigen (keyhole limpet haemocyanin) challenge. No instances of pancytopaenia, aplastic anaemia or bone marrow effects were observed. Furthermore, no increased incidences of infection were observed.

According to the clinical overview and PI, elevations of hepatic transaminases have been observed with sarilumab treatment in clinical trials, but without progression to serious hepatic injury. No elevations of hepatic transaminases were seen in the toxicology studies, even when IL-6 was significantly elevated in the 26 week study in cynomolgus monkeys.

No hypersensitivity reactions (observed in patients), or any effect on organ weights, macroscopic or microscopic pathology, immunophenotypic analysis, or clinical signs, were observed in any of the studies in monkeys. Anti-sarilumab antibodies, developed in monkeys receiving doses of ≤ 15 mg/kg/week, did not cause any apparent toxicological effect. After SC administration, injection sites displayed moderate inflammatory infiltrates (which is not unexpected after SC injection of concentrated human proteins).

Considering the mechanism of action of sarilumab, effects on the immune system may have been anticipated, but there were no sarilumab related effects on the morphology of any organ (including of the immune system). Overall, there was little evidence of toxicity of sarilumab following weekly treatment to monkeys.

Genotoxicity and carcinogenicity

The range and type of genotoxicity studies routinely conducted for small molecule pharmaceuticals are not applicable to biotechnology derived products and therefore, a full battery of tests was not conducted. It is not expected that a monoclonal antibody such as sarilumab would interact directly with DNA or other chromosomal material.

The mechanism of action of sarilumab is not expected to be carcinogenic. No preneoplastic lesions were observed in cynomolgus monkeys administered sarilumab for up to 26 weeks, although this time span is relatively short in the lifespan of this species.

Furthermore, in vivo, sarilumab inhibited the growth of human prostate (Du145 cells) and lung (A549, Calu3 and NCI-H1650 cells) tumour xenografts in immunocompromised mice. Immunohistochemistry analysis of prostate cancer xenografts (DU145 cells) revealed inhibition of growth associated with increased cleaved caspase-3 (marker of apoptosis) immunostaining. Based on these results, and since IL-6 and STAT3 signalling play a role in tumour progression, it is possible that sarilumab treatment may exert an inhibitory effect on the growth of some tumours.

Based on the lack of mechanistic concern, and the data described above, carcinogenicity studies with sarilumab were not considered necessary, consistent with the approach in current regulatory guidelines.

Reproductive toxicity

A fertility study was conducted in mice, in which the effects of inhibition of IL-6Rα on fertility were investigated using the murine specific surrogate REGN844 (sarilumab was not pharmacologically active in rats, mice or guinea pigs). Some additional fertility endpoints (such as reproductive hormones, menstrual cycling and sperm analysis) could have been not included in the repeat dose toxicity studies in cynomolgus monkeys, and an embryofetal development study could have been performed with the surrogate murine antibody.

In the REGN844 study in mice, an increased incidence of implantation site degeneration was observed microscopically at the HD, however no other drug related effects were observed in reproductive indices (mating, fertility and pregnancy), and the significance of the finding is not known.

There was evidence of cross reactivity of sarilumab with (cytoplasm and/or cytoplasmic granule in) human reproductive tissues (prostate, oviduct, cervix, endometrium, placenta) but no evidence from the repeat dose toxicity studies in mice (with REGN844) or cynomolgus monkeys (with sarilumab) of an effect of IL-6Rα block on the reproductive organs of either males or females.

Embryofetal development studies were not conducted in mice or monkeys, and these studies would have been advisable. However, a pre/post-natal development study was performed in monkeys, including dosing since gestation day (GD) GD20, which is the beginning of organogenesis in monkeys (equivalent to Week 3 in a human pregnancy), until GD165 (natural delivery). Exposure began at implantation and continued until at least PND30 at all doses both in mothers and offspring (offspring was then euthanised).

There was no evidence of teratogenicity, although the number of offspring was limited. Offspring were examined for malformations/variations (organ measurements, macroscopic observations and skeletal examination by X-ray imaging).

Increases in pregnancy loss, premature births, stillbirths, neonate deaths post-birth and a decrease in infants surviving to Day 30 to 32 of birth were observed in the 50 mg/kg/week dose group compared to vehicle control and lower dose groups (Table 4).

Table 4: Reproductive toxicity

Finding	Dose (mg/kg/week)			
	0	5	15	50
Abortion/embryofetal death ratio (and percentage)	3/12 (25%)	3/12 (25%)	4/12 (33.3%)	3/12 (25%)
Premature/preterm birth (incidence)	0	0	0	2
Pregnancy loss (and percentage)	5/12 (41.7%)	4/12 (33.3%)	6/12 (50%)	6/12 (50%)
Stillbirth ratio (and percentage)	2/9 (22.2%)(a)	1/9 (11.1%)	2/8 (25%)	3/9 (33.3%)
Neonate deaths post birth	1 (14%)	1 (12%)	1 (14%)	2 (33%)
Infants surviving to BD30-32	6	7	5	4

a = one animal that received emergency C- section due to dystocia and neonate died on Day 2 after birth was included in stillbirth

The study report stated that:

- the stillbirth ratios in the treatment groups were 'comparable' to the testing facility's historical control data (13.6%, ranging from 0 to 33.3%),
- monkeys were observed in a breech delivery position in 1/2 of the stillborn in the control group and in 2/3 of the stillborn in the 50 mg/kg/week group
- it has been reported that around 66% of cynomolgus monkeys in a breech position 1 day before parturition deliver stillborn neonates (rate is only 1% if the animals are in the correct cephalic position); and therefore:
- 'naturally occurring' breech deliveries are a major cause of stillbirth in cynomolgus monkeys.

These arguments, as well as the following facts, may suggest the possibility that the higher stillbirth ratio and total pregnancy loss rates observed in the groups given 50 mg/kg/dose sarilumab could be spontaneous:

- differences were not statistically significant,
- the values were within historical control values, and
- the findings occurred at high systemic exposure margins (≥ 26 times that anticipated at the maximum human dose).

However, the low number of animals in the study does not provide sufficient assurance regarding the validity of the results to inform the conclusion on reproductive safety of sarilumab. The apparent dose response relationship in some of the findings in this study means that the possibility that these findings were actually related to treatment with sarilumab cannot be dismissed. Also, there is no evidence that the 2/3 breech position animals were not somehow related to dysregulation of the IL-6 pathways since they are important for the maintenance of pregnancy (see below). The mechanism behind the trend suggesting embryofetal toxicity is unclear. Nonetheless, there is evidence to suggest that impaired IL-6 activity may affect human reproduction:

- Unlike the leukaemia inhibitory factor (LIF) and IL-11 members of the IL-6 cytokine family, IL-6 is not essential for successful pregnancy, but is likely to play a modulating role during embryo implantation and placental development.
- Genetic IL-6 deficiency is linked with elevated fetal resorption and a delay in parturition in mice.
- Increased IL-6 trans signalling is associated with unexplained infertility.
- Recurrent miscarriage is accompanied by evidence of increased IL-6 trans-signalling systemically, but reduced IL-6 expression in the endometrium.
- Preterm birth is associated with elevated maternal serum and amniotic fluid IL-6, and IL-6 trans-signalling may also be increased.
- In preeclampsia, maternal serum levels of IL-6 are often increased, whereas placental IL-6 production appears decreased,[8] and
- IL-6 expression appears to be a determinant of uterine receptivity at embryo implantation.[9] [10] [11]

[8] Prins JR, Gomez-Lopez N, Robertson SA. Interleukin-6 in pregnancy and gestational disorders. *J Reprod Immunol* 2012; 95: 1–14.
[9] Lim KJ et al (2000). The role of T-helper cytokines in human reproduction. *Fertil Steril*. 2000; 73: 136–142
[10] Jasper MJ et al (2006). Reduced expression of IL-6 and IL-1a mRNAs in secretory phase endometrium of women with recurrent miscarriage. *J Reprod Immunol*. 2006; 73: 74–84

There is a possible contribution of IL-6 to infertility and miscarriage, with evidence that both elevated and diminished IL-6 bioavailability due to altered expression of IL-6 ligand and/or its signalling regulators might contribute to them, perhaps through acting in both stimulating and inhibitory roles in different cell-cell signalling pathways, and presumably depending on the balance of factors, such as interferon (IFN) and toll-like receptor 4 (TLR4) ligands.[6] A complex relationship between IL-6 pathways and reproduction exists, and therefore the apparent absence of (statistically significant) effects on fertility (in mice with REGN844) and pre/postnatal development (in monkeys, with sarilumab) may not necessarily be reflected in humans. In vitro studies indicated that elevated levels of IL-6 impaired implantation[12] and elevated levels were seen in peritoneal fluid of patients with endometriosis[13] and implicated in impairment of ciliary beat frequency in the human Fallopian tube.[14] In animal studies, elevated IL-6 led to apoptosis of germ cells from rats.[15] There may also be species differences in the complex effects of IL-6 on the reproductive system.

Sarilumab's effects observed in monkeys are reminiscent of those of tocilisumab, another IL-6R inhibitor. Administration of tocilizumab in an embryofetal development study in monkeys caused a dose related (but statistically non-significant) increase in the incidence of abortion or embryofetal deaths, at high (≥ 35) relative exposures. This effect was described in the PI document of tocilizumab and that drug was given a Pregnancy Category of C.[16]

In summary, the possibility that due to its pharmacological properties sarilumab causes higher stillbirth ratios and pregnancy loss rates cannot be ruled out. Due to the current uncertainty regarding the causal effects of inhibitors of the IL-6R on stillbirths, embryofoetal deaths, abortion and/or pregnancy loss observed at high doses, it is envisaged that all drugs of this class will receive a Pregnancy Category of C. This category may be reviewed in the future if sufficient clinical evidence or other mechanistic evidence is available.

[11] Sharkey DJ et al (2007). Seminal plasma differentially regulates inflammatory cytokine gene expression in human cervical and vaginal epithelial cells. *Molecular Human Reproduction*. 2007; 13: 491–501.
[12] Smith SK et al (1998:Abstract). The role of leukaemia inhibitory factor and interleukin-6 in human reproduction. *Hum. Reprod*. 1998; 13: 237.
[13] Iwabe T et al (2002). Role of cytokines in endometriosis-associated infertility. *Gynecologic and Obstetric Investigation*. 2002; 53: 19-25.
[14] Papathanasiou A et al (2008). The effect of IL-6 on ciliary beat frequency in the human Fallopian tube. *Am Soc Reprod Med*. 2008; 90: 391-394.
[15] Rival C et al (2006). IL-6 and IL-6 receptor cell expression in testis of rats with autoimmune orchitis. *Reprod Immunol*. 2006; 164.
[16] Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Relative exposure

Table 5: Relative exposure in reproductive toxicity studies

Study, duration and route	Dose (mg/kg/week)	$AUC_{0\text{-}168h}$ (µg.h/mL)	AUC for 2 weeks (µg.h/mL)	Exposure ratio# (over 2 weeks)	
				Based on AUC	Based on dose
TX-08030 Pre-/postnatal development (GD20-GD165) IV	5	37260	74520	8	2.5
	15	124845	249690	26	7.5
	50	396455	792910	84	25
POH0428; (population PK) Rheumatoid arthritis patients	2[a]	-	9480[b]	-	-

= animal:human; a: 200 mg q2w to a 50-kg patient; b: AUC0–14 days of 395 mg.day/L was multiplied by 24 to convert to µg.h/mL; - : not applicable

Exposures in pregnant monkeys were very similar to those in monkeys at the same doses (sexes combined) in the repeat dose toxicity study (26 weeks IV). The relative exposure ratios achieved in cynomolgus monkeys were high. In cynomolgus monkeys, serum sarilumab concentrations were not affected by neutralising antibodies: only 3/12 females at the LD developed anti-sarilumab antibodies, so all animals remained adequately exposed throughout the study.

Pregnancy classification

Placental transfer of sarilumab to the foetus was seen in cynomolgus monkeys, which was consistent with the physiological properties of IgG1 antibodies. Although immunoglobulins can be excreted in milk, sarilumab's excretion in milk was not investigated. It is not certain that infants would be exposed during breast feeding because the protein is likely to be metabolised to smaller peptides before absorption in the gut.

The sponsor has proposed pregnancy Category B2;[17] which is not consistent with tocilizumab another drug of the same class which has a category of C. There were no treatment related adverse findings in fetuses in the cynomolgus monkey infants. Given the long half-life of sarilumab, consideration needs to be given to the newborn if this drug is administered during pregnancy. Although there was no evidence from the monkey study that gestational exposure had an adverse effect on the infants, animal numbers were low.

Since it is likely that owing to its pharmacological effects, sarilumab causes harmful effects on the human fetus or neonate without causing malformations, and in line with the pregnancy category of another drug of the same class displaying similar findings, a pregnancy category of C will be given.

[17] Pregnancy Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Local tolerance

The assessment of local tolerance was incorporated in repeat dose toxicology studies in cynomolgus monkeys by macroscopic and microscopic evaluation of IV infusion and SC injection sites. No findings related to sarilumab administration were observed following IV infusion. In the 3 month SC monkey toxicology study, minimal to moderate perivascular mixed inflammatory cell infiltrates were observed in the dermis and/or the subcutis of sarilumab treated monkeys. The findings, with sarilumab concentrations between 50 and 70 mg/mL, were partially reversible following a 12 week recovery period, and the incidence and severity were not dose dependent.

These findings most likely represent a local reaction to the SC injection of concentrated protein rather than a specific adverse effect of sarilumab per se.

In mice, REGN844 caused only a slight increase in the incidence and severity of mixed inflammatory cell infiltrates at the injection site at ≥ 50 mg/kg/week SC. There were no REGN844-related injection site findings at 10 mg/kg/week SC or 25 mg/kg/week IV.

Paediatric use

Sarilumab is not proposed for paediatric use and no specific studies using sarilumab in juvenile animals were submitted. In a study in mice using a murine surrogate of sarilumab (REGN844), administration of up to 200 mg/kg/week SC to 8 to 10 week old mice for 4 weeks did not cause any observable adverse effect. In juvenile mice treated with REGN844 up to 200 mg/kg/week from PND 14 to sexual maturity (for 9 weeks), there were no observable adverse effects apart from reversible effects associated with the injection of proteinaceous material and/or self-trauma secondary to minor inflammation at the injection site. The no observed adverse effect level (NOAEL) in both murine studies was therefore 200 mg/kg REGN844/week.

Nonclinical summary and conclusions

- An acceptable package of nonclinical studies was submitted, with pivotal toxicology studies conducted in compliance with GLP regulations and with studies broadly in accordance with relevant guidelines.
- Sarilumab (and its murine surrogate) blocked the interaction of IL-6Rα with IL-6, and therefore blocked IL-6-induced receptor signalling. The sarilumab dissociation constant (KD) for human and monkey IL-6Rα was 54 and 123 pM respectively, whereas the dissociation constant of REGN844 (a mouse surrogate IL-6Rα antibody created to support studies in WT mice since sarilumab does not bind to mouse IL-6Rα) for mouse IL-6Rα was 193 pM.
- Sarilumab blocked IL-6 dependent activities by blocking membrane bound and soluble IL-6Rα, and did not have any Fc effector function as assessed with antibody dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) assays.
- Sarilumab (in IL-6/IL-6Rα humanised mice) and REGN844 (in WT mice) inhibited the elevation of an inflammation biomarker (turpentine induced elevation of SAA). REGN844 mitigated inflammation and bone erosion in WT mice with (collagen induced) arthritis. No monkey models of inflammation were evaluated. Increased concentrations of IL-6 were observed in mice and monkeys, supporting the argument that circulating IL-6 cannot bind the receptors since they are blocked by the antibody. REGN844 inhibited the binding of human IL-6 to mouse IL-6Rα (IC50: 4 nM) and the (IL-6 induced) proliferation of a mouse B cell hybridoma cell line (IC50: 110 pM).

Sarilumab/sIL-6R complexes were not biologically active. Dissociation of IL-6 and sIL 6R from their preformed complex in vitro due to sarilumab was not investigated.

- The cynomolgus monkey showed adequate specific cross reactivity with sarilumab in a panel of normal tissues in tissue binding studies. Based on the binding activity, the cynomolgus monkey was appropriately chosen as the main species for toxicity testing.
- Safety pharmacology studies were incorporated with the repeat dose toxicity studies in monkeys. No adverse effects were seen on neurobehavioral parameters, body temperature, or cardiovascular or respiratory effects (including ECG) in monkeys after repeated dosing for up to 26 weeks.
- An acceptable range of pivotal toxicity studies with sarilumab was conducted in one species; the cynomolgus monkey, which was adequately confirmed as a relevant human model in terms of both pharmacodynamic (PD) response to sarilumab and PK. The formulations used in Phase I clinical trials, with excipient profile similar or identical to that proposed for registration were used for all nonclinical studies. No differences in PK or toxicity were observed in monkeys when Phase I and Phase III formulations were compared.
- Serum PK after IV administration of sarilumab were adequately characterised in cynomolgus monkeys. After a single IV dose in monkeys, sarilumab showed limited distribution, slow clearance and a long terminal half-life. There were no sex differences. Accumulation with repeated (weekly) dosing was consistent with the drug's long half-life. Conventional studies of the distribution, metabolism and excretion of sarilumab were not conducted in animals, which is acceptable. There were no nonclinical drug interaction studies. Sarilumab crosses the placenta and is expected to be excreted into milk. Bioavailability after SC dosing was approximately 78% in monkeys after single dosing.
- Anti-sarilumab antibodies were observed in most monkeys receiving 0.5 to 2 mg/kg/week, but generally not in animals receiving ≥ 15 mg/kg/week. Exposure to sarilumab in monkeys was adequate to ascertain its potential toxicity. The draft PI notes the presence of anti-sarilumab antibodies responses, including neutralising antibodies, in 7 to 9% of patients.
- There was no indication from the repeat dose toxicity studies of any target organ toxicity. Even at the highest doses tested in monkeys, sarilumab was well tolerated. In monkeys, the maximum doses used in the SC and IV toxicity studies were up to 25 (based on dose) to 80 (based on AUC) times the exposure in patients. The only effects observed were due to the predictable pharmacological activity of sarilumab as an IL 6Rα inhibitor: moderate and (at least partially) reversible decreases in neutrophil levels, lower primary and secondary IgG responses following an antigen (KLH[18]) challenge, moderate and (at least partially) reversible decreases in serum fibrinogen and serum CRP levels, and reversible increases in circulating IL-6.
- There were no nonclinical studies with sarilumab in combination with other drugs, including MTX.
- The range and type of genotoxicity studies routinely conducted for small molecule pharmaceuticals are not applicable to biotechnology-derived products1 and therefore, a full battery of tests was not conducted. It is not expected that a monoclonal antibody such as sarilumab would interact directly with DNA or other chromosomal material.
- Nonclinical studies investigating genotoxicity or carcinogenicity were not conducted with sarilumab. Sarilumab was not pharmacologically active in mice or rats. Sarilumab

[18] KLH = Keyhole limpet haemocyanin (a T-cell-dependent antigen)

dose dependently inhibited IL-6 induced proliferation of a human B cell line, and in vivo it inhibited the growth of human prostate and lung tumour xenografts in immunocompromised mice. The inhibition of growth in the prostate cancer xenografts was associated with increased cleaved caspase-3 (marker of apoptosis) immunostaining. It is therefore possible that sarilumab treatment may exert an inhibitory effect on the growth of some tumours. No preneoplastic lesions were observed in cynomolgus monkeys administered sarilumab for up to 26 weeks. The mechanism of action of sarilumab is not expected to be carcinogenic.

- The effects of sarilumab per se on male or female fertility, including implantation, were not investigated (there was no evidence for adverse histopathology in reproductive tissues assessed in the 26 week repeat dose toxicity studies, although sarilumab cross reacted with some reproductive tissues; to cytoplasm and/or cytoplasmic granules; in tissue cross reactivity studies). However, no effects on fertility were observed when IL-6Rα block was investigated using the surrogate antibody REGN844 in mice.
- A pre/post-natal development study was performed in pregnant cynomolgus monkeys given IV sarilumab at 5, 15 or 50 mg/kg/week from early organogenesis (Gestation Day (GD) 20) until natural delivery (GD165). There was evidence that sarilumab induced stillbirths and pregnancy loss in cynomolgus monkeys when administered during the period of organogenesis (gestation Day 20 to 165) at doses ≥ 26 fold greater than those recommended in humans (on an AUC basis). While this finding was inconclusive, it could not be ruled out, and has been noted in the draft PI. Treatment with sarilumab had no effect on in-life maternal parameters and no evidence of teratogenicity at doses up to 50 mg/kg/week IV. No adverse effects were observed in dams or infants (the latter were observed for only 30 days after birth). Sarilumab crossed the placenta (expected for an IgG1 antibody) and remained detectable in infant serum until postnatal Day 30 (last measurement day). Excretion into milk was not investigated.
- Studies where REGN844 was administered to juvenile WT mice did not identify particular toxicity related to block of IL-6R in growing animals. Sarilumab is only indicated in adults.

Conclusions and recommendation

- The pharmacology, PK and toxicology of sarilumab were adequately investigated in the submission using appropriate in vitro and in vivo nonclinical models.
- The primary pharmacology studies support the drug's mechanism of action.
- The activity of sarilumab in animal models of rheumatoid arthritis was not investigated. Demonstration of efficacy for the proposed indication will therefore rely on clinical data.
- Haematological effects were the main toxicologically significant findings in cynomolgus monkeys. These were consistent with an exaggerated pharmacological effect arising from interleukin-6 receptor (IL-6R) blockade. These effects were observed at doses significantly greater than the maximum anticipated human dose.
- No target organs of toxicity were identified. Sarilumab is not considered to pose a genotoxic or carcinogenic hazard, and is not teratogenic.
- Sarilumab should not be classified as Pregnancy Category B2 (as proposed by the sponsor) but rather Category C, consistent with that of the currently registered IL-6 blocker, tocilizumab. A trend for increasing adverse outcomes in monkey pregnancies has been observed for both tocilizumab (abortions and/or embryo-foetal deaths) and

sarilumab (stillbirths and pregnancy loss), albeit at high relative exposures for both drugs. Given these findings and the current lack of full understanding of the complexities of IL-6's role in pregnancy, a Pregnancy Category C and a statement of the animal pregnancy findings in the PI is appropriate.

- No nonclinical data were submitted to support the use of sarilumab in combination with MTX and/or other DMARDs. The safety of the use of sarilumab in combination with DMARDs will therefore rely on clinical data.
- There are no nonclinical objections to registration.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 1.

Introduction

Clinical rationale

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. Systemic involvement may also occur, and there is an increased risk of atherosclerosis and lymphoma over time, particularly if the condition is insufficiently controlled. The over-production of pro-inflammatory cytokines such as TNF and IL-6 in the joints and sera of patients with rheumatoid arthritis are important mediators in the disease pathogenesis primarily via activation of T lymphocytes, but also through effects on B lymphocytes. IL-6 can activate hepatocytes to produce acute phase reactants, such as CRP. Sarilumab is a recombinant humanised monoclonal antibody that binds specifically to, and inhibits signalling mediated by both soluble and membrane bound IL-6 receptors. As such, sarilumab treatment inhibits the pro-inflammatory functions of IL-6 at both the intra-articular and systemic level.

Rheumatoid arthritis is a heterogeneous condition in terms of clinical presentation, natural history and drug responsiveness. Published evidence and current guidelines for the treatment of rheumatoid arthritis emphasise the importance of achieving clinical remission, or at least low disease activity, as both of these states are associated with a favourable long term prognosis. Conventional synthetic DMARDs (in particular, MTX), alone or in combination with each other, are the initial recommended treatments for rheumatoid arthritis. Observational studies and meta-analyses of DMARD treatment efficacy and tolerability demonstrate highly variable outcomes to single and combination DMARD therapy over time. In 10 year follow-up studies, 25% of patients with rheumatoid arthritis had to discontinue conventional DMARD treatment due to insufficient therapeutic benefit and 20% discontinued treatment due to adverse effects. Biological DMARDs, either as add-on or single drug therapy, is the next recommended line of therapy in active rheumatoid arthritis after conventional synthetic DMARD failure or intolerability. While anti-TNF drugs and cytokine modulators such as abatacept have been shown to demonstrate significant efficacy in treating active rheumatoid arthritis, 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 response rates range from 50 to 65% and ACR50 response rates are 35 to 50%.[19] In Australia, an alternative biological therapy (tocilizumab) targeting IL-6 signalling is already approved for use in rheumatoid arthritis. Tocilizumab was first approved in Australia in May 2009 for the treatment of moderate to severe active rheumatoid arthritis in adult patients. In October 2010, the treatment indication was extended to include inhibition of the progression of joint damage, as measured by X-ray, when given in combination with MTX. In October 2011 and February 2014 (respectively), the indication for tocilizumab was further extended to include systemic, and thereafter, polyarticular juvenile idiopathic arthritis in patients aged 2 years and older. In this submission, the sponsor claims for there is an unmet need for additional therapies for active, treatment refractory rheumatoid arthritis in adult patients. In particular, sarilumab is a monoclonal antibody therapy that has a different mechanism of action to conventional DMARDs and the most commonly used biological DMARDs, anti-TNF drugs.

Guidance

There is one specific EU guideline adopted by the TGA relevant to this submission, besides the general guidelines:

- CPMP/EWP/556/95 Rev 1: Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. Effective: 29 January 2007

Contents of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies for sarilumab in adult patients with rheumatoid arthritis and contained the following clinical information:

- 9 clinical pharmacology studies, including 8 that provided PK data and 1 that provided PD data.
- 4 population PK analyses of pooled rheumatoid arthritis patient data (Studies POH0428, POH0455, POH0429 and POH0446).
- 2 pivotal efficacy/safety studies (Part B of Study EFC11072 and Study EFC10832).
- 1 dose finding study (Part A of Study EFC11072).
- 5 other efficacy/safety studies were considered as part of this submission including Study LTS11210 (an ongoing, long term safety study); Study SFY13370 (safety calibrator trial of sarilumab versus tocilizumab); Study EFC11574 (a Phase III trial of sarilumab + MTX versus etanercept + MTX in adult patients with rheumatoid arthritis who had an inadequate response to 4 months of adalimumab + MTX; study was prematurely ceased), Study MSC12665 (study supporting use of auto-injector device) and Study ACT11575 (Phase II trial of sarilumab + MTX versus golimumab + MTX in adult patients with rheumatoid arthritis; study was prematurely ceased).

[19] The ACR20/ACR50/ACR50 is a composite measure defined as:

- An improvement of 20%/50%/70% in the number of tender and number of swollen joints; and
- A 20%/50%/70% improvement in 3/5 of the following criteria: patient global assessment, physician global assessment, functional ability measure (such as the Health Assessment Questionnaire (HAQ)), visual analog pain scale (VAS), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

American College of Rheumatology Committee to Re-evaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. Arthritis Rheum. 2007 Mar 15;57(2):193-202.

- No pooled analyses or meta-analyses of efficacy were provided, but integrated summaries of efficacy and safety across the pivotal trials were included (examining for outcome consistency and subgroup factors).
- Study EFC13752 (an open label immunogenicity and safety trial of sarilumab in adult patients with active rheumatoid arthritis) was included in the sponsor submission, but not considered by the evaluator as the current application is for sarilumab therapy in combination with non-biologic DMARDs.
- 3 ongoing Phase III studies (Studies EFC14059, LTS13618 and PDY14191) in Japanese subjects and for the purpose of supporting registration in Japan have provided interim serious adverse event (SAE) data only in this submission.

Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Biopharmaceutical Studies and associated Analytical Methods, Summary of Clinical Pharmacology Studies and literature references (n = 118).

Paediatric data

The submission did not include paediatric data. However, a paediatric development program for sarilumab is ongoing, and the sponsor intends to submit an application to support use in children upon completion of the clinical development program around June 2022.

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

The PK of sarilumab has been well characterised from the PK data collected from 53 healthy subjects involved in 1 Phase I study; 241 adult patients with rheumatoid arthritis enrolled in 8 Phase I studies and 2,671 patients with rheumatoid arthritis involved in 7 Phase II/III studies of sarilumab treatment. This dataset includes a total of 1,770 patients with rheumatoid arthritis who have received any dose of sarilumab. Regarding the 2 proposed commercial doses of sarilumab, the PK dataset includes 631 patients who have received sarilumab 150 mg therapy and 682 subjects treated with sarilumab 200 mg q2w for up to 52 weeks. Table 6 displays a summary of the clinical studies in humans relating to each PK topic. None of the PK studies had deficiencies that excluded their results from consideration.

In addition to the observed data, the sponsor has conducted 4 pre-specified population PK and population PK/PD analyses using pooled data from Phase I, II and III studies. Table 6 summarises the population PK/PD analyses that have been conducted with sarilumab and included in this submission. None of the population PK/PD analyses had deficiencies that excluded their results from consideration.

Table 6: Summary of submitted clinical pharmacology studies (PK and PD) with sarilumab

Study type	Study identifier	Sarilumab dose regimen	Population	Number enrolled[i]
Biopharmaceutic studies (Phase 1)				
Single dose, comparative bioavailability	TDU11373[a]	100, 150, and 200 mg; a single SC dose	Healthy subjects	53
Single dose, comparative bioavailability	PKM12058[a]	200 mg; a single SC dose	RA patients	32
Pharmacokinetics and initial tolerability studies in patients (Phase 1)				
Single ascending dose IV	TDU10808/ 6R88-RA-0703	0.6 and 2.0 mg/kg; a single IV dose	RA patients	7[b]
Single ascending dose SC	TDU10809/ 6R88-RA-0801	50, 100, and 200 mg; a single SC dose	RA patients	15
Repeat ascending dose SC	TDR10805/ 6R88-RA-0802	50, 100, and 150 mg qw; 100, 150, and 200 mg q2w	RA patients	60
Intrinsic factors (Phase 1, population PK analysis)				
Race (Japanese)	TDU13402[c]	50, 100, and 200 mg; a single SC dose	RA patients	24
Age, gender, body weight, race, laboratory measurements.	POH0428[d]	50, 100, 150, and 200 mg, a single SC dose; 100, 150, and 200 mg q2w SC; 50, 100, and 150 mg qw SC	Pooled RA patients	1770
Extrinsic factors (Phases 1, 2, and 3 population PK analysis)				
Prior biologics, methotrexate	POH0428[d]	50, 100, 150, and 200 mg; a single SC dose	Pooled RA patients	1770
		100, 150, and 200 mg q2w SC; 50, 100, and 150 mg qw SC		
Effect of sarilumab on other drugs (Phase 1)				
Simvastatin (CYP3A4 substrate)	INT12684 Part A[e]	200 mg; a single SC dose	RA patients, MTX-IR	19
PD and PK/PD studies (Phase 1)				
PD for biomarkers, PK/PD for key safety parameters, biomarkers[f]	ACT10804/ 6R88-RA-0803	50, 100, and 200 mg; a single SC dose	RA patients	32
	6R88-RA-1309	150 and 200 mg; a single SC dose	RA patients	101[g]
Pharmacokinetics in efficacy/safety studies (Phases 2 and 3)				
Phase 2	EFC11072 Part A	100, 150, and 200 mg q2w; 100 and 150 mg qw SC	RA patients, MTX-IR	306
Phase 3[e]	EFC11072 Part B	150 and 200 mg q2w SC	RA patients, MTX-IR	172 (Cohort 1) 1197 (Cohort 2)[h]
	EFC10832	150 and 200 mg q2w SC	RA patients, TNF-IR	546
	SFY13370	150 and 200 mg q2w SC	RA patients, TNF-IR	202[i]
	MSC12665[a]	150 and 200 mg q2w SC	RA patients, DMARD-IR	217
	EFC13752	150 and 200 mg q2w SC	RA patients, DMARD-IR	132
	LTS11210	150 and 200 mg q2w SC	RA patients who completed or transferred from 1 of 6 previous sarilumab trials	2008

Table 6: (continued) Summary of submitted clinical pharmacology studies (PK and PD) with sarilumab

Population PK and population PK/PD in clinical pharmacology and efficacy/safety studies				
Population PK	POH0428[d]	50, 100, 150, and 200 mg, a single SC dose; 100, 150, and 200 mg q2w SC; 100 and 150 mg qw SC	Pooled RA	1770
PK/PD for key efficacy and safety parameters	POH0455[j]	100, 150 and 200 mg q2w SC; 100 and 150 mg qw SC	Pooled RA patients	2221
Population PK/PD for absolute neutrophil count	POH0429[k]	50, 100, 150, and 200 mg, a single SC dose; 100, 150, and 200 mg q2w SC; 50, 100, and 150 mg qw SC	Pooled RA patients	1672
Population PK/PD for DAS28-CRP	POH0446[k]	100, 150 and 200 mg q2w SC; 100 and 150 mg qw SC	Pooled RA patients	2082

a Studies TDU11373, PKM12058, and MSC12665 are summarized in 2.7.1 for PK comparability of drug products/presentations
b Two to 4 patients were enrolled in Cohort 2 (2.0 mg/kg sarilumab) because of early termination.
c The study was conducted in Japan in Japanese patients with RA.
d Population PK analysis used data from Phase 1, 2, and 3 studies in patients with RA.
e Studies INT12684 Part B, EFC11574, EFC14092, and ACT11575 were excluded due to lack of available PK data.
f Biomarkers were C-reactive protein, interleukin 6, soluble interleukin 6 receptor, serum amyloid A, the erythrocyte sedimentation rate, and/or fibrinogen.
g Of the total listed, 25 and 24 patients were randomized and treated with 4 and 8 mg/kg tocilzilumab, respectively.
h Cohort 1 consisted of patients who were randomized prior to dose selection for Phase 3. Cohort 2 consisted of patients randomized after dose selection for Phase 3 in this operationally seamless Phase 2/3 study.
i 102 of 202 patients were randomized to the 4 mg/kg tocilzilumab group.
j Population PK/PD analysis of pooled data from Phase 2 and 3 studies in patients with RA.
k Population PK/PD analysis of pooled data from Phase 1, 2 and 3 studies in patients with RA.
l N in pooled population PK or PK/PD analyses was the number of patients in the analysis data set

CYP3A4: cytochrome P450, subfamily III, polypeptide 4; DAS28: disease activity score for 28 joints; DMARD: disease modifying antirheumatic drug; MTX-IR: methotrexate inadequate responder; na: not applicable; PD: pharmacodynamic(s); PK: pharmacokinetic(s); qw: every week; q2w: every 2 weeks; RA: rheumatoid arthritis; TNF-IR: tumor necrosis factor alpha antagonist inadequate responder;

For the full evaluation of the PK and PD data please see Attachment 1, extract from the clinical evaluation report.

Evaluator's conclusions on pharmacokinetics

The PK of sarilumab in adult patients with active rheumatoid arthritis has been well characterised in the studies included in this submission. Sarilumab exhibits nonlinear PK with target mediated drug disposition. It is well absorbed after SC administration (T_{max} of 2 to 4 days and estimated bioavailability of 80%), exhibits a low apparent volume of distribution (7.3 L) and undergoes elimination by parallel linear and nonlinear pathways. At higher serum concentrations, elimination is predominantly through the linear, non-saturable proteolytic pathway and at a lower drug concentration; the nonlinear saturable target mediated elimination pathway predominates. The elimination pathways result in an initial half-life of 8 to 10 days and a terminal concentration dependent half-life of 2 to 4 days. After the last steady state doses of sarilumab 150 once every 2 weeks (q2w) and 200 mg q2w therapy, the median times to non-detectable drug concentrations are 28 and 43 days, respectively. Sarilumab exposure increases in a greater than dose proportional manner. The main source of intrinsic PK variability identified in patients using population PK analysis is body weight, with an increase in weight resulting in reduced drug exposure. No other demographic characteristics (age, ethnicity or gender) have a significant effect on the PK of sarilumab. There is no data in patients with severe renal or hepatic impairment. The concomitant administration of low dose oral MTX has no effect on the PK of sarilumab, nor does prior biologic DMARD treatment. However, exposure of simvastatin (a sensitive CYP3A4 substrate) decreases by 45% when co administered with a single SC dose of sarilumab 200 mg. This finding is consistent with inhibition of IL-6 signalling resulting in restoration of cytochrome P450 (CYP) activity, leading to increased metabolism of drugs

that are CYP substrates. The effect of sarilumab on CYP enzymes may be clinically relevant for a CYP substrate with a narrow therapeutic index.

Positive anti-drug antibody (ADA) status has a significant impact on the PK of sarilumab resulting in a 24 to 28% lower drug exposure when compared to ADA negative patients. If patients exhibit a persistently positive response to ADA then drug exposure is even lower (by 32 to 41%) than in patients with transient positive ADA response. sarilumab concentrations of neutralising antibody positive patients appeared to be even lower versus neutralising antibody negative patients (by 49 to 59%).

Pharmacodynamics

Studies providing pharmacodynamic data

The ability of sarilumab to bind and capture circulating IL-6 has been formally validated in several clinical studies involving adult patients with active rheumatoid arthritis. The PD effect of sarilumab has been primarily assessed by the measurement of several serum inflammatory markers and serum sIL-6R. Total sIL-6R can be regarded as a biomarker for sarilumab and is indicative of target engagement. Total sIL-6R is defined as free IL-6R plus IL-6R complexed with sarilumab after drug exposure.

In this submission, the sponsor has presented PD data collected in 5 Phase I studies (Studies TDU10808/6R88-RA-0703, TDU10809/6R88-RA-0801, TDR10805/6R88-RA-0802, ACT10804/6R88-RA-0803 and 6R88-RA-1309), 1 Phase II study (Study EFC11072 Part A) and 2 Phase III studies (Part B of Study EFC11072 and Study EFC10832). The PD dataset is supported by 3 population PK/PD analyses (Studies POH0455, POH0429 and POH0446), which modelled data from various clinical trials to cover a broad range of dosing regimens in adult patients with active rheumatoid arthritis. A summary of the studies providing PD data is included in Table 6 (shown above). None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

In this submission, the PD properties of sarilumab when used in adult patients aged > 18 years with active rheumatoid arthritis was assessed from data collected in 5 Phase I studies, 3 Phase II-III trials and 3 population PK-PD analyses. The studies involved > 2,000 patients who received sarilumab by SC injection across a broad dose range (from a single dose of 50 mg to 150 mg once weekly (qw)). In the pivotal Phase III study (Part B of Study EFC11072), drug exposure for up to 52 weeks of therapy has been evaluated. The sponsor has appropriately nominated mean changes in serum total IL-6R and sIL-6R levels as the primary PD markers of interest for sarilumab. Mean or median serum changes in serum inflammatory markers (CRP, SAA, fibrinogen and erythrocyte sedimentation ratio (ESR)) were evaluated as the secondary PD biomarkers of relevance. Expectedly for the mechanism of action of sarilumab, the pivotal and supporting studies demonstrated a rapid and dramatic decrease in serum CRP within 2 to 4 days of first drug administration. The median time to nadir CRP levels is 7 days. Other acute phase reactants such as SAA and fibrinogen levels follow a similar time course of effect. CRP levels return to near normal 15 to 30 days after last drug administration. With repeat sarilumab dosing by SC administration, CRP levels reach steady state by Week 24 and remain at the same level up to Week 52 of therapy. The mean values for free sIL-6R decreased rapidly (2 weeks) following SC administration of sarilumab and remained constant thereafter for extended periods of follow-up (at least 24 to 52 weeks).

Reductions in free sIL-6R, CRP and other PD biomarkers, all correlated with sarilumab exposure and were accompanied by efficacy improvements. Over the 153 fold

concentration range following qw (100 and 150 mg qw) and q2w (100, 150, and 200 mg q2w) dose regimens in the Phase II study, the effect on free sIL-6R and CRP levels, and efficacy endpoints (ACR20, ACR50, and ACR70 scores; and the DAS28-CRP;[20]) was apparent only at drug concentrations achieved with doses of 150 mg q2w or above. A plateau was reached for all endpoints at the sarilumab concentration for the 200 mg q2w dose, with further increase in exposure by as much 2.7 fold (150 mg qw) providing no significant incremental change in response. The Phase II study also showed a greater reduction in neutrophil counts with increasing sarilumab up to 200 mg q2w. The PK/PD analyses supported the conclusion from the dose response relationships that the 150 and 200 mg q2w doses were appropriate for the Phase III program. In the Phase III studies, both 150 and 200 mg q2w doses showed near maximal suppression of serum CRP levels, but there was potentially more rebound toward Baseline near the end of the dosing interval for the sarilumab 150 mg q2w dose than for the 200 mg q2w dose, suggesting that suppression of IL-6 signalling may be more complete with sarilumab 200 mg q2w therapy. In the pivotal Phase III studies, CRP levels decreased to within the normal range (< 10 mg/L) and SAA levels were < 20 mg/L when the trough concentration of sarilumab was above 1 mg/L. The combined Phase III trial dataset shows that a higher percentage of patients treated with SC sarilumab 200 mg q2w had sarilumab trough concentrations above 1 mg/L by Week 24 (86%) than patients treated with SC sarilumab 150 mg q2w (61%). The sponsor considers this finding as a pivotal piece of evidence in justifying the proposed posology of 200 mg q2w.

The PK/PD relationships for safety endpoints (neutropaenia, elevated serum alanine transaminase (ALT) values and raised low density lipoprotein (LDL) levels) showed a higher rate of adverse effects with an increasing sarilumab concentration, but the effect reached a plateau at the lower concentration range observed with sarilumab 150 mg q2w therapy, apart from neutropaenia. Mean decreases in the neutrophil count from Baseline were predicted to be greater for sarilumab 200 mg q2w therapy versus sarilumab 150 mg q2w dosing (39% versus 31%), and there was also a small increased risk of severe neutropaenia (that is neutrophil count < 1.0 x 10^9/L) occurring in patients at the median concentration for sarilumab 200 mg q2w therapy when compared to the median concentration with sarilumab 150 mg q2w treatment.

Dosage selection for the pivotal studies

Dose selection for the Phase III clinical study program started with interpretation of the PK and PD data from single and multiple dose studies in adult patients with active rheumatoid arthritis taking concomitant MTX. This data informed the dose selections and regimens of sarilumab (to be used concomitantly with MTX) to be investigated in the double blind, placebo controlled Phase II trial (Part A of Study EFC11072).

The selected doses and regimens of sarilumab in that dose finding study were those considered to have the potential to suppress PD markers, such as CRP, SAA and fibrinogen, throughout the dosing interval.

Part A of Study EFC11072 was a 12 week, 6 arm, dose ranging study intended to select the 2 dose regimens of sarilumab for further evaluation in the Phase III program. In Part A, subjects were randomly assigned in a ratio of 1:1:1:1:1:1 to receive either placebo injections qw, sarilumab 100 mg qw, sarilumab 150 mg qw, sarilumab 100 mg q2w, sarilumab 150 mg q2w or sarilumab 200 mg q2w. The maximum duration of study involvement for each individual patient was 22 weeks (up to 4 weeks of screening, followed by 12 weeks for study treatment and 6 weeks of follow-up after their last

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

injection). The complete set of efficacy results reported in Part A of Study EFC11072 is detailed in Attachment 1. Patients from Part A of Study EFC11072 did not participate in Part B of the trial. However, subjects who completed Part A were eligible to enter an open label, long term extension, Study LTS11210.

The dose regimens of sarilumab investigated in both of the pivotal Phase III trials (Part B of Study EFC11072 and EFC10832) were selected on the results obtained during the Phase I and II programs. Clinical efficacy results from Part A of Study EFC11072 concluded that 4 doses of sarilumab (150 mg q2w, 200 mg q2w, 100 mg qw and 150 mg qw) showed efficacy in the adult rheumatoid arthritis patient population. There was no clear dose response relationship for the incidence of treatment emergent adverse events (TEAE) and serious adverse events (SAEs) were infrequent in all treatment groups. The lowest sarilumab dose with efficacy (150 mg q2w) and a second dose regimen (200 mg q2w) were chosen for evaluation in the pivotal Phase III trials based on the benefit-risk ratio analysis. In addition, the sponsor states that from the perspective of patient convenience, a less frequent injection schedule is preferred (q2w versus qw).

Both of the pivotal Phase III trials were placebo controlled for the first 12 to 16 weeks. However, 35 to 39% of placebo treated patients (versus 13 to 14% of sarilumab treated subjects) were transferred to rescue therapy with sarilumab before Week 24 because of insufficient clinical response. In addition to placebo or sarilumab injections, all patients in both trials received concurrent non-biological DMARDs (> 90% of which was weekly low dose oral MTX). The mean and median doses of concomitant background treatment with conventional DMARD therapy (predominately MTX) was consistent with contemporary clinical practice in Australia. However, recent expert opinion concludes that such prior therapy reflects sub-optimal practice before the commencement of biologic therapy in patients with active rheumatoid arthritis.[21] In particular, the maximal concurrent dose of MTX should be used in the comparator arm of all biologic therapy trials (up to 25 mg/week, by the SC route if dose > 15 mg/week for MTX) as sub-optimal MTX dose in the comparator arm may bias efficacy results in favour of biological agents. Moreover, low dose oral corticosteroid (prednisone > 10 mg/day) and non-steroidal anti-inflammatory drug (NSAID) use was recorded in approximately two-thirds of all patients (equally dispersed among the treatment arms) in the 2 pivotal sarilumab studies, which reflects appropriate concomitant drug use in individuals with active rheumatoid arthritis, and is consistent with prescribing patterns in Australia.

Efficacy

Studies providing efficacy data

There were 2 pivotal Phase III trials (Part B of Study EFC11072 and Study EFC10832) in support of the application for the treatment of rheumatoid arthritis with sarilumab. Both of the Phase III studies were of similar design; randomised, double blind, parallel group, placebo controlled trials in adult patients with active rheumatoid arthritis. Both of the Phase III trials examined the effect of sarilumab 150 mg and 200 mg injections given by SC injection q2w when added to non-biologic DMARD therapy (mostly, weekly low dose oral MTX). The main difference between the 2 pivotal Phase III studies was the recruitment of subjects with a preceding inadequate response to MTX in Study EFC11072 versus subjects who were inadequate responders or intolerant of anti-TNF therapy in Study EFC10832.

[21] Duran J et al, 2016 Methotrexate dosage as a source of bias in biological trials in rheumatoid arthritis: a systematic review. *Ann Rheum Dis* 2016; 75: 1595-1598.

For the full presentation of the evaluation of efficacy please see Attachment 1.

Evaluator's conclusions on efficacy

In support of the proposal for sarilumab to be granted a treatment indication in active rheumatoid arthritis in conjunction with non-biologic DMARDs, this submission contains two pivotal Phase III studies (Part B of Study EFC11072 and EFC10832) of similar design, as well as one supportive Phase II trial (Part A of Study EFC11072) and a long term, open label extension trial (Study LTS11210). The pivotal efficacy studies were of 24 to 52 weeks duration and enrolled a total of 1,743 patients for efficacy analysis. A total of 306 patients were enrolled in the dose finding Phase II trial of up to 22 weeks duration, and the ongoing, long term, open label study (with up to 5 years of treatment follow-up planned) has enrolled 1,914 subjects, and thus far followed these subjects for 2 to 4 years.

Both of the Phase III studies were randomised, double blinded and placebo controlled in design and enrolled adult patients with a confirmed diagnosis of rheumatoid arthritis according to the appropriate classification criteria. Subjects were required to have moderate to severe disease activity at Baseline with the tender joint count being ≥ 8 and the swollen joint count being ≥ 6 and CRP being > 6 to 10 mg/L, despite at least 3 to 6 months of treatment with non-biologic DMARDs (typically MTX monotherapy) and/or stable doses of NSAID and/or low dose corticosteroids (CS). The Phase III studies were of similar design with the main difference being the recruitment of subjects with a history of inadequate response or intolerance to anti-TNF drugs into Study EFC10832 versus subjects with a preceding inadequate response to MTX in Part B of Study EFC11072. Both of the Phase III trials examined the effect of 2 doses of sarilumab (150 mg and 200 mg injections q2w by SC injection) compared to placebo injections plus continued background therapy with oral, non-biologic DMARDs.

The baseline demographic and disease related characteristics of patients in both of the Phase III trials are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. The majority of patients were female, of Caucasian ethnicity, and within the expected age range of 25 to 65 years. Approximately one-fifth of all recruited subjects were current smokers, which is a factor associated with diminished response to treatment. However, there are some caveats to the generalisability of the treatment population. For example, both studies excluded patients who were at a significant risk of infection (particularly, tuberculosis) or malignancy, or who had various abnormal laboratory results at Baseline (for example abnormal haematology, liver function tests or lipid parameters). In addition, a history of inflammatory bowel disease, severe diverticulitis and previous gastrointestinal perforation were exclusion criteria. At randomisation, patients were stratified on the basis of whether they were anti-TNF naïve or anti-TNF experienced. As per protocol, all 546 patients recruited into Study EFC10832 had a history of anti-TNF exposure (92.3% inadequate response) and 27.4% (328/1197) of all subjects recruited into Part B of Study EFC11072 had a history of anti-TNF exposure.

Studies EFC11072 Part B (Cohort 2) and EFC10832 shared 2 co-primary endpoints: the proportion of patients who achieved an ACR20 response at Week 24 and the mean change from Baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) score (at Week 16 in Part B of Study EFC11072 [Cohort 2] and at Week 12 in Study EFC10832). The mean change from Baseline in the modified Total Sharp Score (mTSS) at Week 52 was the third co-primary endpoint in Study EFC11072 (Part B, Cohort 2). The key secondary efficacy endpoint in Study EFC11072 (Part B, Cohort 2) was the proportion of patients who achieved a major clinical response (MCR) (defined as ACR70 response maintained for at least 24 consecutive weeks during the 52 week trial period). In both pivotal studies, various secondary endpoints were evaluated to further describe the clinical response (such as the rates of ACR50 and ACR70 response), improvements in physical function and

to explore the impact of sarilumab upon health related quality-of-life (QOL). The ACR response criteria are a composite of clinical (tender and swollen joint counts), biochemical (CRP) and subjective assessments (pain, physician global and patient global) determining response to therapy in patients with rheumatoid arthritis. Recent evidence supports the use of the ACR composite criteria as the preferred measure of accurately determining response in rheumatoid arthritis with other measures such as Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and Boolean criteria being also valuable.[22] Evidence using DAS28 criteria may not be as reliable and should only be used in supporting the other measures.

This submission is seeking an indication in active rheumatoid arthritis and is consistent with the relevant TGA adopted regulatory guideline.[23] Both of the Phase III trials included patients who had previously been exposed to anti-TNF drugs, and also those who were anti-TNF naïve (Part B of Study EFC11072 only). For both Phase III studies, the choice of efficacy endpoints and statistical analysis were appropriately performed; and strategies to maintain blinding and randomisation procedures were suitable.

In Part B of Study EFC11072, where sarilumab 150 mg and 200 mg injections, given q2w by SC injection were compared with placebo injections plus concurrent non-biological DMARDs, and the 3 co-primary efficacy endpoints showed a statistically superior response with both doses of sarilumab therapy versus placebo. Overall, 58.0% (232/400) of patients treated with sarilumab 150 mg q2w and 66.4% (265/399) of subjects treated with sarilumab 200 mg injections achieved an ACR20 response at 24 weeks versus 33.4% (133/398) of patients in the placebo group. The mean change from Baseline to Week 16 in the HAQ-DI score was also statistically greater in patients treated with sarilumab (-0.54 for the 150 mg group and -0.58 for the 200 mg arm) than in subjects treated with placebo (-0.30). At Week 52, smaller increases from Baseline in the mTSS were observed in subjects treated with sarilumab (0.90 for the 150 mg group and 0.25 for the 200 mg arm) than in patients treated with placebo (2.78), indicating relative inhibition of progression of structural damage with sarilumab treatment. The key secondary efficacy endpoint of Part B of Study EFC11072 was MCR, which is defined as achieving and maintaining an ACR70 response for at least 24 consecutive weeks during the 52 week trial period. A higher proportion of patients in the sarilumab treatment groups achieved MCR (12.8% (51/400) in the 150 mg group and 14.8% (59/399) in the 200 mg arm) compared to placebo (3.0%; 12/398). Many secondary efficacy measures of clinical relevance such as rates of higher level ACR (50 and 70) as well as CDAI response at 24 weeks, as well as the mean change from Baseline in the HAQ-DI score confirmed that sarilumab is effective in treating the symptoms and signs of active rheumatoid arthritis as well improving physical functioning. Improvements in health related QOL were also beneficially attained with sarilumab therapy.

In Study EFC10832 (where anti-TNF experienced subjects were enrolled), both doses of sarilumab showed statistically significant benefit over placebo treatment for the rate of ACR20 response at Week 24 and the mean change from Baseline to Week 12 in the HAQ-DI score. Many of the ranked secondary endpoints in the hierarchical testing strategy (which controlled for multiplicity of testing with adjusted p-values) supported the benefit of both doses of sarilumab over placebo at Week 24.

Neither of the pivotal Phase III studies were designed or powered to evaluate for potentially significant differences in clinical response between the 2 sarilumab dose regimens. This is major deficiency of the current submission, particularly because the sponsor is requesting registration of the higher dose regimen for the majority of patients.

[22] Smolen J, et al. Clinical trials of new drugs for the treatment of rheumatoid arthritis: focus on early disease. *Ann Rheum Dis* 2016; doi: 10.1136/annrheumdis-2016-209429.
[23] EU guideline CPMP/EWP/556/95 rev1 "Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for the Treatment of Rheumatoid Arthritis" (effective 29 January 2007)

The Phase III study data also shows that sarilumab 150 mg and 200 mg therapy given by SC injection q2w is effective in treating anti-TNF naïve as well as anti-TNF experienced patients. In the pooled subgroup analyses, high subject weight at Baseline (> 100 kg) appeared to be associated with significantly lower ACR20 response rates for sarilumab 150 mg treatment, which were not statistically better than placebo + DMARD therapy.

The clinical efficacy data available up to Week 216 in the long term extension Study LTS11210 shows that the majority of responding patients appear to maintain their treatment related benefit with continued sarilumab therapy. In addition, for placebo patients who switched to sarilumab at Week 12 to 24, the rate of ACR responses recorded over time in the open label trial were similar to those achieved in the originally treated sarilumab cohort.

The supporting Phase II trial (Part A of Study EFC11072) showed that treatment with sarilumab 150 mg/week was superior to placebo for the rate of ACR20 response at Week 12 (72.0% (36/50) for sarilumab versus 46.2% (24/52) for placebo). Statistically significant ACR20 response rates were not demonstrated in any of the other sarilumab dose groups compared to placebo, although there was a trend towards treatment effect with 4 other sarilumab dose regimens (including 150 mg q2w and 200 mg q2w).

Overall, the data in this submission supports the efficacy of sarilumab therapy in combination with non-biological DMARDs (particularly, weekly low dose oral MTX) for the treatment of rheumatoid arthritis in those with moderate to severely active disease at Baseline. The dataset demonstrates that sarilumab is effective in both anti-TNF naïve and anti-TNF experienced subjects. The magnitude of clinical response with sarilumab is similar to that observed in the pivotal studies, which supported the registration of biologic therapies in rheumatoid arthritis.

The posology of sarilumab is an issue of difference with the sponsor submission. Sarilumab 150 mg by SC injection (given every 2 weeks) appears to be the lowest, most clinically effective dosing regimen in adult patients with rheumatoid arthritis. The sponsor requested dose of sarilumab therapy for most patients (200 mg q2w) has not demonstrated clinically meaningful superiority for efficacy outcomes over sarilumab 150 mg q2w.

Safety

Studies providing safety data

The following dose response and non-pivotal efficacy/safety studies provided safety data:

- Part A of Study EFC11072 (dose finding trial) provided safety data regarding overall AEs, AEs of special interest (for example injection site reactions), blood parameters (haematology and liver function tests), physical examination and anti-drug antibodies.
- Study LTS11210, which is the ongoing, long term extension trial of sarilumab therapy in adult patients with rheumatoid arthritis provided AE data up to Week 216 of therapy.
- Study SFY13370 was a randomised, double blind safety calibrator trial which assessed the safety and tolerability of sarilumab versus tocilizumab over 24 weeks.

Other studies evaluable for safety only:

- Study MSC12665 has provided usability and tolerability data on SC sarilumab therapy administered by auto-injector device or prefilled syringe.

- Study ACT11575 (prematurely ceased Phase II trial with 16 enrolled subjects) contributed 7 sarilumab treated patients into the long term Study LTS11210.
- Study EFC11574 (prematurely ceased Phase III trial with 43 enrolled subjects) contributed 16 sarilumab treated patients into the long term Study LTS11210.
- 9 clinical pharmacology studies provided safety data regarding overall AEs, AEs of special interest (for example injection site reactions), blood parameters (haematology and liver function tests), physical examination and anti-drug antibodies.

A total of 9 Phase I, clinical pharmacology studies have been conducted with sarilumab. One study (Study TDU11373) was conducted in healthy subjects and the remaining studies were conducted in adult patients with rheumatoid arthritis. Of the 8 studies conducted in patients with rheumatoid arthritis, in 1 single dose Study TDU10808/6R88-RA-0703) sarilumab was administered IV and in the remaining trials, sarilumab was administered by SC injection. Of the 7 studies in which sarilumab was given SC, 1 was a repeat dose study (Study TDR10805/6R88-RA-0802) and all the other trials were single dose studies. The key AE data for the clinical pharmacology studies was provided in the in the overall AE section the CER (see Attachment 1).

Patient exposure

The primary safety database supporting this submission consists of 3 completed studies (Studies EFC11072, EFC10832 and SFY13370) and 2 terminated studies (Studies ACT11575 and EFC11574). All 5 studies were Phase II and III trials. Studies ACT11575 and EFC11574 were terminated early due to delays in their starting and the impact on the overall sarilumab development timeline rather than any identified safety concerns with sarilumab. Patients in Studies EFC11072, EFC10832, EFC13752, SFY13370 and ACT11575 were able to enrol into an open label, uncontrolled extension study (Study LTS11210), which is ongoing. Patients in Studies EFC11072 and EFC10832 could initiate rescue therapy with open label sarilumab (initially 150 mg qw before Phase III dose selection and thereafter 200 mg q2w. The submission contains another ongoing study (Study MSC12665), which is evaluating the usability of auto-injector device (AID) and pre-filled syringe (PFS) in adult patients with active rheumatoid arthritis who are candidates for open label sarilumab therapy.

A total of 2,887 patients have received at least 1 dose of sarilumab + non-biologic DMARD therapy in the Phase II and III rheumatoid arthritis clinical development program, providing 4,338.9 patient years (PY) of cumulative drug exposure. At the commercially proposed sarilumab dose of 200 mg q2w, approximately 1,200 patients have received at least 48 weeks of drug exposure. At both doses of sarilumab (200 mg q2w and 150 mg q2w), over 1,650 patients have received at least 48 weeks of drug exposure. In the placebo controlled population, 661 patients have received sarilumab 200 mg q2w + DMARDs for a total exposure of 425.5 PY, 660 patients have received sarilumab 150 mg q2w + DMARDs for a total exposure of 425.8 PY and 661 subjects have received placebo injections + DMARDs for a total of 373.1 PY. The duration of double blind treatment was longer in the 2 sarilumab treatment groups due to the higher proportion of placebo subjects switching to open label rescue treatment with sarilumab.

Safety issues with the potential for major regulatory impact

Liver toxicity

Sarilumab therapy is associated with an increased frequency of elevated serum transaminases compared to placebo in the first 12 to 24 weeks of therapy. There appears to be a consistent dose related relationship between raised serum ALT and/or aspartate aminotransferase (AST) values with sarilumab therapy. However, the abnormalities of

liver function often resolved with continued sarilumab treatment and no cases meet the clinical criteria for Hy's law. Further details regarding abnormal liver function tests are presented in Attachment 1.

Haematological toxicity

Drug related neutropaenia is an identified safety risk with anti-IL-6 therapy. Based on central laboratory analyses in the Phase III trials, the incidence of neutropaenia is up to 16% in the first 24 weeks of therapy and the frequency was higher with the higher dose of sarilumab treatment (200 mg q2w therapy). Over the extended treatment follow-up period, the annual incidence of Grade 2 or higher neutropaenia appears to plateau and largely resolve with sarilumab dose reduction to 150 mg q2w therapy. Further details regarding neutropaenia are presented in Attachment 1.

Risk of serious and opportunistic infection

Sarilumab therapy is associated with a potential increased risk of infection, including herpes zoster infection and latent tuberculosis. Meticulous screening for tuberculosis was an entry requirement of all the Phase II and III studies in this submission. No patient in the Phase II-III trials developed reactivation of latent tuberculosis. Herpetic infections were reported at a low but increased frequency in both pivotal studies with sarilumab treatment, and the observation was not dose dependent. Furthermore, the overall rate of infection related SAEs was higher in sarilumab treated subjects versus placebo patients.

Cardiovascular safety and elevation of lipid profiles

Patients with rheumatoid arthritis are known to be at an increased risk of major adverse cardiac events (MACE). A total of 28 MACE events in 26 patients have been recorded in the rheumatoid arthritis trials included in this submission. There were 10 cases were non-fatal myocardial infarction and 7 reports of non-fatal stroke (equally dispersed among the sarilumab dose groups). Seven MACE related deaths were adjudicated to have occurred. The overall rate of MACE is low at 0.6 per 100 PY, which is within expectations for the target population.

Unwanted immunological events

The rate and consequences of developing anti-sarilumab antibodies has been discussed in sections 8.5.5 and 4.2.3 of Attachment 1. However, the development of ADA does not appear to be clearly associated with loss or lack of efficacy, nor the occurrence of AEs (any specific type or overall incidence). Nonetheless, there is increased plasma clearance of sarilumab in the presence of ADA, which requires ongoing pharmacovigilance, particularly for the loss of efficacy outcomes.

In this submission, no subjects developed clinical consequences consistent with systemic autoimmune disease (such as systemic lupus erythematosus) or major neurologic disorders.

Safety in special populations

Subgroup analyses of the long term sarilumab safety population have revealed potential risk factors for some specific types of AEs. There is a higher incidence of neutrophil cell count < 1.0 x 109/L in subjects with a lower baseline neutrophil count (< 6.0 x 109/L) and in those weighing < 60 kg. The incidence of neutropaenia in those with a baseline count < 6.0 x 109/L is 8.6% (32/370) for sarilumab 150 mg q2w + DMARD therapy (versus 2.8% (8/289) if baseline > 6.0 x 109/L) and 13.2% (46/348) for sarilumab 200 mg q2w + DMARDs (versus 4.8% (15/313) if baseline > 6.0 x 109/L). The incidence of neutropaenia in those weighing < 60 kg is 14.4% (31/215) for sarilumab 150 mg q2w + DMARD therapy (versus 5.0% if weighing > 60 kg) and 16.7% (44/264) for sarilumab 200 mg q2w + DMARDs (versus 7.5% if weighing > 60 kg). A higher incidence of ALT > 3 x upper limit of

normal (ULN) was seen in patients whose baseline ALT was > ULN, those with a duration of rheumatoid arthritis < 3 years, patients enrolled in South America centres and in subjects with no prior biologic exposure. A higher frequency of serious infection was observed in patients on sarilumab whose weight was > 100 kg or receiving weekly MTX dose > 20 mg. CS use, which has been shown to be associated with an increase in infections in rheumatoid arthritis, was included in the analyses, and only a small difference was observed in any sarilumab dose group in the long term safety population between patients who were on baseline CS and those who were not (5.9% versus 4.8%). Elderly patients (age > 65 years) are at an increased risk of infection (overall and serious) regardless of therapy (placebo or any sarilumab dose).

In the long term safety population, 9 patients became pregnant and 1 male patient's partner became pregnant. Of the 9 patients who became pregnant 4 subjects experienced spontaneous miscarriage (all of which occurred during the first trimester; 2 of whom had a prior history of spontaneous or unspecified abortion), 3 patients delivered healthy children and the other 2 subjects had an estimated date of delivery after the data cut-off date of this submission. Similarly, the patient's partner who became pregnant had an estimated date of delivery after the data cut-off date.

There is no available information on the safety of sarilumab in the setting of live vaccines, and with self-administration of medication.[24]

Postmarketing data

Not applicable.

Evaluator's conclusions on safety

In this submission, the total clinical safety dataset for the use of sarilumab (any dose) in adult patients with active rheumatoid arthritis consists of 4,339 PY of drug exposure with 1,546 patients receiving treatment for > 48 weeks, 1,020 subjects receiving therapy for > 96 weeks and 624 patients exposed for > 144 weeks. In terms of the sarilumab doses being requested for approval in this submission, 660 patients have received 150 mg q2w therapy (425.8 PY of exposure) and 661 patients have received 200 mg q2w treatment (425.5 PY of exposure) in the placebo controlled population (versus 661 patients in the control arms; 373.1 PY of exposure). In the pivotal Phase III study (Part B of Study EFC11072), the median duration of exposure to sarilumab was 364 days. In the Phase III rheumatoid arthritis program, sarilumab therapy was given by SC injection either at a dose of 150 mg or 200 mg q2w. Both of the proposed doses in rheumatoid arthritis (150 mg and 200 mg) had more than 600 subjects exposed to sarilumab for at least 6 months. More than 95% of patients in the rheumatoid arthritis dataset received concurrent MTX, more than 70% were taking concomitant NSAIDs, and approximately half were taking concurrent low dose oral CS. Overall, there is a sufficient volume of data to make a meaningful assessment of sarilumab safety for up to 100 weeks of treatment in the newly proposed treatment indication of active rheumatoid arthritis.

Compared to placebo, a higher incidence of overall AEs, SAEs and AEs resulting in permanent treatment discontinuation were observed in sarilumab treatment groups, with some of the AE types occurring at a higher incidence in the higher dose sarilumab treatment cohort (200 mg q2w versus 150 mg q2w). Mortality rates were similar between sarilumab and placebo therapy in short term treatment follow-up.

Infection was the most common AE recognised with sarilumab and these occurred at a higher frequency in the sarilumab treatment groups versus control during the true

[24] The sponsor subsequently provided information on the safety of sarilumab with self-administration of medication. Please see Attachment 1 Section 12; Question 5.

placebo controlled treatment periods (12 to 16 weeks for both pivotal trials). The majority of infections were mild in severity, self-limiting, and were predominately either upper respiratory tract infection (URTI), urinary tract infection or nasopharyngitis. 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 weight > 100 kg was associated with a higher incidence of overall and infection related AEs. In the integrated placebo controlled population, the exposure adjusted rate of serious infection is 5.5 events per 100 PY (95% CI 3.30, 7.82) in the sarilumab 200 mg q2w treated patients, 3.6 events per 100 PY (95% CI 2.08, 5.90) in the sarilumab 150 mg q2w subjects and 3.9 events per 100 PY (95% CI 2.20, 6.47) in the control group. In the sarilumab + DMARD long term safety population, the exposure adjusted event rate is slightly lower than that observed in the placebo controlled population at 4.3 events per 100 PY (95% CI 3.35, 5.35) in the sarilumab 200 mg q2w group, which remains higher than that in the sarilumab 150 mg q2w dose group (3.1 events per 100 PY; 95% CI 1.96, 4.75). No patients developed reactivation of latent tuberculosis in the sarilumab clinical study program. However, there was an increased risk of oral herpes virus infections with sarilumab versus placebo. This finding may be expected given the role of IL-6 in protective immunity. A sarilumab dose effect was also observed for the risk of herpes zoster infection. The majority of herpetic infections were rated as mild or moderate in severity, responded to standard treatment and did not result in permanent discontinuation from sarilumab.

Hypersensitivity reactions were an uncommon type of AE reported at a slightly higher incidence in patients receiving sarilumab (with no dose response relationship) compared to placebo therapy. Most hypersensitivity AEs were non-specific reports of rash, which were rated as mild in severity, resolved without specific intervention and did not result in discontinuation from sarilumab. Only 4 potential systemic hypersensitivity reactions were reported with sarilumab in the total rheumatoid arthritis safety dataset. Discontinuations due to AEs occurred at a higher frequency in sarilumab versus placebo treated subjects.

A total of 25 deaths (22 in sarilumab treated subjects) have been reported in patients with rheumatoid arthritis in the long term safety population, including 7 MACE related deaths. The rate of malignancies in the RA dataset is within expectations of the treatment population and the types of cancer observed did not identify any specific safety signals with sarilumab. However, longer periods of treatment follow-up are required to inform about this potential safety concern.

Neutropaenia is a recognised safety concern with anti-IL-6 therapy and the issue was identified with sarilumab in the rheumatoid arthritis treatment studies. In the short term period (first 16 weeks) of both pivotal Phase III studies, the overall incidence of neutropaenia was higher in both sarilumab treatment groups compared with placebo. The approximate overall incidences of neutropaenia were 10.0 to 16.0% for sarilumab (with a dose response relationship observed for 150 mg and 200 mg therapy) versus 1.0% for placebo. There were several cases of Grade 3 or 4 neutropaenia observed in both sarilumab treatment groups and over the long term follow-up period of the Phase III studies, the incidence of neutropaenia was up to 20% with sarilumab. The majority of neutropaenic episodes were transient and not associated with infection related AEs. There were also several cases of significant thrombocytopaenia observed in patients treated with sarilumab.

The total safety dataset also identified 2 other abnormalities of laboratory values which occurred at a numerically higher frequency in the sarilumab treatment cohorts compared with placebo. Elevations in hepatic transaminases and dyslipidaemia have been associated with sarilumab versus placebo. Again, both of these abnormalities appear to display a dose response relationship with sarilumab. In general, patients who developed increases in liver function tests had changes of mild-moderate severity which were transient in nature and without associated clinical sequelae.

The incidence of rheumatoid arthritis subjects developing new anti-drug antibodies to sarilumab is low at < 10% at 52 weeks in the pivotal Phase III trial 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.

In summary, the safety data indicates that sarilumab has an acceptable overall safety profile up to 52 weeks of therapy in the treatment of adult patients with moderately to severely active rheumatoid arthritis. There is limited long term safety data in the current submission to assess the risk of some types of AEs such as malignancy and MACE, which will require additional longitudinal safety follow-up. From the clinical evaluator's assessment of the safety dataset, there are some significant safety concerns with sarilumab therapy including the risk of infection, opportunistic infection (mainly oral herpes viral and zoster infection), hypersensitivity reactions, neutropaenia, thrombocytopaenia, abnormal liver function tests and dyslipidaemia. These safety concerns are consistent with the known profile of anti-IL-6 therapy in adult patients with rheumatoid arthritis. Significant pharmacovigilance will be required if approval is granted for registration of sarilumab for the treatment of rheumatoid arthritis. This would include vigilance for opportunistic infections, MACE and malignancy (particularly, non-melanoma skin cancers).

First round benefit-risk assessment

First round assessment of benefits

The benefits of sarilumab in adult patients with moderately to severely active rheumatoid arthritis in the proposed usage (200 mg, once q2w, given by SC injection; or 150 mg every 2 weeks if certain laboratory abnormalities) are:

- Improvement in the signs and symptoms of rheumatoid arthritis (as per the ACR clinical response criteria), which appear to be maintained to at least 52 weeks of treatment.
- Improvement in physical functioning (as evidenced by treatment related improvements in the HAQ-DI scale).
- sarilumab therapy is associated with a statistically lower rate of structural disease progression at 52 and 100 weeks of treatment as measured by serial plain X-rays of the peripheral joints affected by rheumatoid arthritis.
- Concurrent use of non-biologic DMARDs (mainly, weekly low dose oral MTX) with sarilumab was presented in the current submission and the efficacy outcomes with sarilumab monotherapy are not available at present.
- In the population of subjects enrolled into Study EFC10832 (that is inadequate response or intolerance of previous anti-TNF therapy), a statistically higher rate of ACR20 response at 24 weeks and improvement in HAQ-DI score at 16 weeks was demonstrated with both doses of sarilumab versus placebo injection + oral DMARD therapy.
- The benefits demonstrated with sarilumab versus placebo extend to various patient subgroups (age, gender, race, region and baseline disease severity) although being seronegative for rheumatoid factor (RF) was associated with lower ACR response rates.
- Sarilumab therapy improves various health related quality of life outcomes.
- Convenient dosing schedule (once every 2 weeks) using a convenient mode of administration (SC injection via prefilled syringe).

First round assessment of risks

The risks of sarilumab in the proposed usage include:

- Increased incidence of overall infection compared to placebo, which are usually minor in severity (in particular, urinary tract infection and URTI), but there is also an increased risk of serious infection with sarilumab.
- Increased risk of pneumonia and various types of herpes infection (oral and zoster) with sarilumab 200 mg q2w therapy.
- Increased risk of drug induced neutropaenia and thrombocytopaenia compared to placebo.
- Risk of precipitation of gastrointestinal perforation and aggravation of diverticulitis.
- Increased frequency of raised serum transaminases and atherogenic serum lipid profiles compared to placebo.
- Potential increased risk of malignancy and MACE requiring long term surveillance; not evident in the current short to medium term safety dataset.
- Higher rates of injection site reactions with sarilumab versus placebo injections, which are usually non-severe in nature and rarely lead to permanent treatment discontinuation.
- Increased rates of permanent treatment discontinuation with sarilumab versus control treatment (placebo injections + oral DMARDs) due to a combination of infections and abnormal investigation results.
- Live vaccines cannot be given concurrently with sarilumab.
- Sarilumab has not been studied in patients < 18 years of age, in subjects with significant organ dysfunction (including renal, hepatic or cardiac failure), those at risk of reactivated latent tuberculosis (requiring meticulous screening at Baseline) and in pregnant or lactating women.

First round assessment of benefit-risk balance

The overall benefit-risk balance of sarilumab in combination with non-biologic DMARDs (mainly, weekly low dose oral MTX) in adult patients with moderately to severely active rheumatoid arthritis, who have had an inadequate response to 1 or more DMARDs, is favourable. Although there are several biologic therapies approved for the treatment of rheumatoid arthritis, including an alternative drug targeting IL-6 inhibition (tocilizumab), a significant proportion of patients still do not achieve optimal or adequate efficacy when one considers clinically meaningful measures of improvement, such as the rates of ACR20 and ACR50 response. Other limitations to currently available therapies in Australia include diminished efficacy over time and drug related safety concerns such as opportunistic infection (including tuberculosis (TB)), malignancy (for example lymphoma) and various laboratory test abnormalities (for example abnormal liver function tests and cytopaenia). Thus, there remains a significant unmet need for new drugs with unique mechanisms that can provide a rapid onset of effect, as well as improved and sustained symptom improvement and a safety profile that allows for long term use.

Sarilumab is a fully human IgG1 monoclonal antibody that selectively binds to both soluble and membrane bound IL-6 receptors, thereby neutralising the effects of the pro-inflammatory cytokine, IL-6. IL-6 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses, but the cytokine also plays a key role in the pathogenesis of rheumatoid arthritis. In this submission, sarilumab has been evaluated in a large clinical program, which complied with CHMP guidelines for evaluation of treatment

in rheumatoid arthritis.[25] The clinical studies have evaluated an adequate number of subjects in the target patient population and demonstrated that sarilumab is an effective in the treatment of active rheumatoid arthritis. For most patients with rheumatoid arthritis, the minimum most effective dose of sarilumab therapy is 150 mg q2w by SC injection, however, the sponsor is proposing 200 mg q2w as the primary commercial dose because it shows numerically higher efficacy for ACR50 and ACR70 responses and questionably superior inhibition of X-ray progression, but none of this clinical data has been subject to pre-specified statistical testing. Nonetheless, the superior efficacy of sarilumab versus placebo (in conjunction with non-biologic DMARDs, mainly MTX) was consistent in most patient subgroups. Subjects with a body weight > 100 kg appeared to have better clinical response to the higher dose of sarilumab (200 mg injections) but the sponsor has not requested a dose modification in this patient subgroup.

The safety profile of sarilumab observed in the clinical study program is consistent with that known for tocilizumab, based on the anticipated effects of IL-6 inhibition, including an increased risk of infection and changes in certain laboratory parameters, in particular, decreases in neutrophil count and increases in hepatic transaminases and serum lipids. Sarilumab is a monoclonal antibody given by SC injection, thus the occurrence of ADA was also expected. The risk profile of sarilumab is based on a total of 1,220 sarilumab treated patients with rheumatoid arthritis involved in the 2 pivotal Phase III studies, as well as additional safety information collected from approximately 3,000 patients treated with any dose of sarilumab.

In the rheumatoid arthritis trials, there was an increased incidence in overall infections in the 2 sarilumab dose groups compared to placebo, with a slightly increased frequency of infection with the highest dose of sarilumab (200 mg therapy). The majority of reported infections were mild or moderate, upper respiratory tract and urinary infections. Herpes related infections were also more frequent with sarilumab (in a possible dose dependent relationship) compared to placebo. However, very few serious opportunistic infections were reported with sarilumab.

Neutropaenia was much more frequently observed with sarilumab than placebo, but most cases were of mild severity (CTCAE Grade 1 or 2), transient and reversible. More severe neutropenia (CTCAE Grade 3-4) was also more frequently observed with sarilumab, but were rarely associated with serious infection. There was also an increased incidence of mild-moderate hepatic transaminase elevations and dyslipidaemia with sarilumab versus placebo, which was not clearly dose related.

Malignancy represents a theoretical risk with any immunosuppressive therapy, but there is no evidence that sarilumab confers an increased risk for malignancy in the current dataset of medium term drug exposure. In the submitted trials, sarilumab treatment was associated with a higher incidence of injection site reactions compared to placebo, but these were generally mild, localised and self-limiting. Importantly, there were only a handful of cases of serious hypersensitivity reactions and no cases of anaphylaxis were recorded.

The laboratory changes associated with sarilumab are typical for IL-6 inhibition, including decreases in neutrophil and platelet count, and increases in serum transaminases and lipids. These were observed more frequently for sarilumab treatment groups compared to placebo. Significant changes in laboratory parameters associated with sarilumab were managed by dose modification from 200 mg q2w to 150 mg q2w. The submission contained a subset of patients who experienced dose modification for the above problems and no clinical consequences of sarilumab dose reduction were observed. Changes in abnormal laboratory results generally stabilised after 4 weeks. Furthermore, the sponsor is proposing routine laboratory monitoring to consist of neutrophil count, platelet count,

[25] CHMP; Committee for Medicinal Products for Human Use

liver function tests and lipid profile within 4 to 8 weeks of initiating sarilumab therapy, and then every 3 months thereafter (6 months for lipid profile).

First round recommendation regarding authorisation

The clinical evaluator recommended acceptance of the sponsor's request for the registration of sarilumab for the treatment of moderately to severely active RA in adult patients who have failed to respond to or are intolerant of 1 or more DMARD drugs (including prior anti-TNF therapy). The treatment indication reflects the populations studied in the submitted trials. The proposed wording also includes specification that sarilumab treatment should only be used in combination with non-biological DMARDs, which is consistent with the submitted dataset. The current submission provides robust evidence that sarilumab is effective in improving the symptoms and signs of active RA as well as physical functioning, and potentially slowing the progression of structural joint damage.

However, the clinical evaluator does not agree with the sponsor proposed posology for sarilumab therapy, which recommends 200 mg q2w as the regimen for the majority of patients, and the dose of sarilumab can be reduced to 150 mg q2w for the management of neutropenia, thrombocytopenia and elevated liver enzyme tests. The clinical evaluator recommends the posology of sarilumab be 150 mg q2w for all patients as the totality of the clinical dataset indicates that this is the lowest, most clinically effective regimen.

Regarding justification for the proposed sarilumab posology, 2 dose regimens (sarilumab 150 mg q2w and sarilumab 200 mg q2w by SC injection) were selected for investigation in the two Phase III studies. Both doses achieved similar ACR20 response rates at 24 weeks of therapy. The sponsor states that the sarilumab 200 mg dose had numerically higher ACR50 and ACR70 response rates at 24 weeks, but these findings has not been subject to pre-specified statistical testing nor were the studies powered for such an analysis. The sponsor asserts that a higher percentage of patients receiving 200 mg versus 150 mg sarilumab therapy obtain serum sarilumab concentrations at the end of the dosing interval which equate with clinical response. Furthermore, analyses of the PD data (mainly CRP results) suggest that suppression of IL-6 signalling was more complete at the end of the dosing interval in patients treated with sarilumab 200 mg q2w versus 150 mg q2w. The sponsor proposes that while sarilumab 150 mg q2w therapy may be sufficient for managing the signs and symptoms of rheumatoid arthritis, pharmacology data indicates more effective suppression of IL-6 signalling throughout the dosing interval is obtained with sarilumab 200 mg q2w. The sponsor also hypothesises that more complete suppression of IL-6 may lead to greater inhibition of structural progression of the disease, as well as greater improvements in other clinical endpoints. However, the pharmacology data has not been supported by the appropriate supporting analysis of the clinical efficacy data showing superiority of sarilumab 200 mg q2w over 150 mg q2w.

Should approval of the sponsor's proposed registration of sarilumab for the treatment of active rheumatoid arthritis be granted, the clinical evaluator also recommended that approval 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 long term Study LTS11210.

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

For details of the clinical questions, the sponsor's responses and the evaluation of these responses please see Attachment 1.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of sarilumab for the treatment of adult patients with active in the proposed usage are similar to those identified in the first round assessment of benefits. The Phase III studies are well conducted trials, which demonstrate a robust and clinically meaningful efficacy benefit with sarilumab versus placebo for improving the symptoms and signs of active RA as well as improving physical function in a second or third line treatment population (that is after failure to adequately respond to 1 or more DMARDs, including biologic therapy) when combined with MTX. Study EFC11072 was able to demonstrate a statistically significant benefit with both doses of sarilumab versus placebo for the inhibition of joint structural progression as determined by sequential plain X-rays of peripheral joints, but the clinical relevance of this observation is unclear. Regarding the proposed dosing regimen, the clinical efficacy data (in particular, the rate of ACR20 response and X-ray outcomes) does not support the higher posology of 200 mg q2w (versus 150 mg q2w) as the minimal, clinically effective regimen. Because of the limitations of post hoc analyses, the efficacy response data provided in the response to questions does not support a robust scientific claim of additional benefit with the higher dose versus lower dose regimen. On the current dataset, the evaluator recommends that the lower dose sarilumab regimen (150 mg q2w) be solely considered for registration.

Second round assessment of risks

After consideration of the responses to the clinical questions (principally, question 5) (see Attachment 1), the risks of sarilumab are unchanged from those identified in the first round. The observed pattern of study drug injections by performer (study site staff, professional caregiver and patient or non-professional person at home) shows a comparable incidence and type of AEs between the two drug administration groups (professional versus non-professional injectors) apart from a slightly higher frequency of minor injection site reactions (erythema and pruritus), which is unlikely to be of clinical significance and impact upon the overall benefit: risk assessment.

Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, there is no change to the opinion expressed in the first round. The overall benefit-risk balance of sarilumab injections in the proposed treatment indication of active RA in adult patients is favourable. Clinically relevant, robust efficacy (with respect to improving the symptoms and signs of RA, as well as physical function) has been observed with sarilumab in combination with MTX. Patients recruited into the Phase III studies were inadequate responders to conventional and/or biologic DMARD therapy. Unfavourable effects consistent with the expected profile of an anti-IL-6 therapy have been observed with sarilumab, including serious infections and cases of neutropenia.

Second round recommendation regarding authorisation

The evaluator recommended acceptance of the sponsor's request for the registration of sarilumab for the treatment of moderately to severely active RA in adult patients who have failed to respond to or are intolerant of 1 or more DMARD drugs (including prior anti-TNF therapy). The treatment indication reflects the populations studied in the submitted trials. The proposed wording also includes specification that sarilumab treatment should only be used in combination with non-biological DMARDs, which is consistent with the submitted dataset. Based on the data available, sarilumab in combination with MTX is effective and demonstrates a comparable and an acceptable safety profile to other biologic therapies (including an alternative anti-IL-6 therapy, tocilizumab) in the management of active RA in adult patients. However, on the balance of scientific evidence, the sponsor proposed posology for sarilumab is insufficiently acceptable. The sponsor proposed posology for sarilumab therapy recommends 200 mg q2w as the regimen for the majority of patients, and the dose of sarilumab can be reduced to 150 mg q2w for the management of neutropenia, thrombocytopenia and elevated liver enzyme tests. The evaluator recommends the posology of sarilumab be 150 mg q2w for all patients as the totality of the clinical dataset indicates that this is the lowest, most clinically effective regimen with an acceptable safety profile.

Should approval of the sponsor's proposed registration of sarilumab for the treatment of active RA be granted, the evaluator also recommends that approval be subject to regular periodic safety update reports and when available, the sponsor provides the TGA with the final clinical study report for the long term Study LTS11210.

VI. Pharmacovigilance findings

Risk management plan

The sponsor has submitted EU-RMP version 1.0 (dated 9 June 2016, data lock point (DLP) 17 February 2016) and Australian Specific Annex (ASA) version 3.0 (dated 14 November 2016) in support of this application.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 7.

Table 7: Summary of the proposed summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns (ASA v3.0)		Pharmacovigilance		Risk Minimisation	
		Routine[26]	Additional	Routine[27]	Additional
Important identified risks	Serious infections	√	√ §	√	√
	*Hypersensitivity reactions**	√*	§	√*	√*
Important potential risks	Increased risk of infection secondary to neutropaenia	√	§	√	√
	Thrombocytopaenia and potential risk of bleeding	√	§	√	√
	Clinically evident hepatic injury	√	§	√	√
	Impact on cardiovascular (CV) outcome (major adverse cardiac event (MACE)) secondary to low density lipoprotein (LDL) elevation	√	√ §	√	√
	Gastrointestinal (GI) perforations	√	√ §	√	√
	Malignancy	√	√	√	-
	Clinical consequences of immunogenicity	√	-	√	-
	*Demyelinating disorders**	√*	-*	x*	-*
Missing information	Use in pregnant and lactating women	√	√	√	-
	Use in paediatric patients	√	-	√	-
	Use in patients with	√	-	√	-

[26] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[27] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Summary of safety concerns (ASA v3.0)		Pharmacovigilance		Risk Minimisation	
		Routine[26]	Additional	Routine[27]	Additional
	*hepatic impairment**				
	*Use in patients with renal impairment**	√	-*	√*	-*
	*Long term use**	√*	√*	x*	-*
	*Use in patients switching to/from other drugs in the anti-IL-6R class**	√*	-*	x*	-*

Additions (all changes since ASA v1.0) are italicised and denoted with asterisks (*); §: Knowledge and Understanding Surveys of HCPs and patients listed as additional pharmacovigilance for this concern (that is a measure of the effectiveness of the risk minimisation activities); X: No risk minimisation is proposed in the PI, however 'Prescription only medicine' status is stated as routine risk minimisation for this concern. *: Safety concern specific to Australia, not included in the EU-RMP summary of safety concerns

- Additional pharmacovigilance activities proposed by the sponsor were:
  - North American Pregnancy registry to monitor risks in the missing information concern of 'use in pregnant women'.
  - A knowledge and understanding survey in HCPs and patients in Europe post launch to evaluate the effectiveness of risk minimisation measures.
  - Paediatric investigational plans (for polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis, proposed in the EU-RMP).
- Additional pharmacovigilance activities proposed by the sponsor in response to recommendations made in the evaluation are:
  - A Safety surveillance program using existing EU rheumatoid arthritis registries.
  - A knowledge and understanding survey in HCPs and Patients post-launch in Australia to evaluate the effectiveness of risk minimisation measures.
  - Study LTS11210 (EXTEND): A study to evaluate long term safety.
- The proposed routine and additional risk minimisation activities are:
  - PI, CMI and Package insert: 'Instructions for use' for patients.
  - A health care professional guide to educate prescribers and pharmacists on actions to minimise specific identified risks.
  - Patient Alert Card.

Post second round (Pre-ACPM) advice to the Delegate

The sponsor has adequately addressed the recommendations in the second round risk management plan (RMP) evaluation.

The RMP evaluator has no objection to the implementation of the current RMP.

Minor recommendations

The sponsor should implement a targeted follow-up questionnaire to provide structured investigation of all reported cases of malignancies, but specifically to allow further characterisation of the risk of skin cancers.

Outstanding minor commitments

The sponsor has committed to providing the knowledge and understanding survey study plans and final draft education materials for TGA review prior to launch.

The sponsor has committed to provide a comparison, in the ASA, of the risk minimisation content in the EU-SmPC;[28] and PI texts addressing each safety concern when the EU-SmPC is finalised.

Wording for conditions of registration

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

The suggested wording is:

> Implement EU-RMP version 1.0 (9 June 2016, data lock point 17 February 2016) with Australian Specific Annex version 3.0 (14 November 2016), submitted with application PM-2015-04024-1-3, and any future updates and a condition of registration.

VII. Overall conclusion and risk/benefit assessment

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

Introduction

This submission is to register a new biological medicine, sarilumab, under the product names Kevzara and Ilsidex by the sponsor. Sarilumab is an IgG1 monoclonal antibody that binds to IL-6, similar to tocilizumab (Actemra), for the treatment of moderate to severe rheumatoid arthritis in combination with non-biological disease-modifying anti-rheumatic drugs (DMARDs). The sponsor is requesting 2 strengths of 200 mg and 150 mg that are to be administered SC q2w. The submission is clinically supported by two Phase III studies over 24 to 52 weeks, along with a number of other studies, in adult patients who have had an inadequate response or intolerance to one or more DMARDs. The requested indication is for combination use only with non-biological DMARDs and a further submission is planned for monotherapy use at a later date pending the results of an additional study. The development program for Kevzara was guided by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) requirements.

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. Systemic involvement may also occur, and there is an increased risk of atherosclerosis and lymphoma over time, particularly if the condition is insufficiently controlled. The over-production of pro

[28] EU-SmPC: European summary of product characteristics

inflammatory cytokines such as TNF and IL-6 in the joints and sera of patients with rheumatoid arthritis are important mediators in the disease pathogenesis primarily via activation of T lymphocytes, but also through effects on B lymphocytes. IL-6 can activate hepatocytes to produce acute phase reactants, such as CRP. Sarilumab is a recombinant humanised monoclonal antibody that binds specifically to, and inhibits signalling mediated by both soluble and membrane-bound IL-6 receptors.

Sarilumab has not been previously considered by ACPM.

Kevzara has not yet been approved [at the time of writing the first request for advice from the ACPM] anywhere internationally and is under evaluation in Canada (submitted January 2016) and Europe (submitted July 2016). It was submitted to the US FDA in October 2015 and a complete response letter was issued by the FDA on 28 October 2016 indicating the submission could not be approved due to manufacturing facility deficiencies. A copy of this letter is included in the agenda and the sponsor has been requested to provide an update in their response.

The requested indication in the USA is:

> *'Kevzara is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more Disease-Modifying Anti Rheumatic Drugs (DMARDs)'.*

The proposed (US) dosage is 200 mg once every 2 weeks.

Quality

The quality evaluator has no objections to approval on quality grounds and has recommended batch release testing as a condition of registration. Kevzara is a clear, colourless to pale yellow, aqueous-buffered sterile solution of pH 6.0. The SC injection is supplied as a single-use prefilled syringe in 2 strengths, 131.6 mg/mL and 175 mg/mL, providing doses of 150 mg and 200 mg, respectively. Sarilumab is produced by recombinant CHO cells that have been engineered to constitutively express sarilumab heavy and light chains in culture. All manufacturing steps and analytical procedures have at present been validated but the issue raised by the FDA is being considered. The proposed shelf life is 2 years when stored at 2 to 8°C, protected from light. The proposed shelf life and storage condition for the product out of the fridge is 14 days when stored at room temperature. There was a number of outstanding GMP licences that the sponsor needed to follow up on prior to registration.

Nonclinical

The nonclinical evaluator has no objections to the registration of Kevzara. The pharmacology, PK and toxicology of sarilumab were adequately investigated in the submission using appropriate in vitro and in vivo nonclinical models. The primary pharmacology studies support the drug's mechanism of action however the activity of sarilumab in animal models of rheumatoid arthritis was not investigated. Haematological effects were the main toxicologically significant findings in cynomolgus monkeys. These were consistent with an exaggerated pharmacological effect arising from IL-6R blockade. These effects were observed at doses significantly greater than the maximum anticipated human dose. No target organs of toxicity were identified. Sarilumab is not considered to pose a genotoxic or carcinogenic hazard, and is not teratogenic. No nonclinical data were submitted to support the use of sarilumab in combination with MTX and/or other DMARDs, therefore this will rely on clinical data.

The sponsor has requested a Pregnancy Category B2, however the evaluator considers Category C, consistent with that of the currently registered IL-6 blocker tocilizumab, to be appropriate. A trend for increasing adverse outcomes in monkey pregnancies has been observed for both tocilizumab (abortions and/or embryofetal deaths) and sarilumab (stillbirths and pregnancy loss), albeit at high relative exposures for both drugs. Given these findings and the current lack of full understanding of the complexities of IL-6's role in pregnancy, a Pregnancy Category C and a statement of the animal pregnancy findings in the PI is recommended.

Clinical

The clinical dossier included the following data:

- 9 clinical pharmacology studies.
- 4 population PK analyses of pooled rheumatoid arthritis patient data (Studies POH0428, POH0455, POH0429 and POH0446).
- 2 pivotal clinical studies (Part B of Study EFC11072 and Study EFC10832).
- 1 dose-finding study (Part A of Study EFC11072).
- 5 other efficacy/safety studies:
  - Study LTS11210 (an ongoing, long term safety study)
  - Study SFY13370 (a safety calibrator trial of sarilumab versus tocilizumab)
  - Study EFC11574 (a Phase III trial of sarilumab + MTX versus etanercept + MTX in adult patients with rheumatoid arthritis who had an inadequate response to 4 months of adalimumab + MTX; this study was prematurely ceased)
  - Study MSC12665 (a study of the auto-injector device)
  - Study ACT11575 (a Phase II trial of sarilumab + MTX versus golimumab + MTX in adult patients with rheumatoid arthritis; this study was prematurely ceased).
- Study EFC13752 (an open label immunogenicity and safety trial of sarilumab in adult patients with active rheumatoid arthritis).
- 3 ongoing Phase III studies (Studies EFC14059, LTS13618 and PDY14191) in Japanese subjects.

Pharmacokinetics

Sarilumab exhibits nonlinear PK with target mediated drug disposition. It is well absorbed after SC administration (T_{max} of 2 to 4 days and estimated bioavailability of 80%) and exhibits a low apparent volume of distribution (7.3 L). At higher serum concentrations, elimination is predominantly through the linear, non-saturable proteolytic pathway and at a lower drug concentration through the nonlinear saturable target mediated elimination pathway. The elimination pathways result in an initial half-life of 8 to 10 days and a terminal concentration dependent half-life of 2 to 4 days. After the last steady state doses of sarilumab 150 q2w and 200 mg q2w therapy, the median times to non-detectable drug concentrations are 28 and 43 days, respectively. The main source of intrinsic PK variability identified in patients using population PK analysis is body weight, with an increase in weight resulting in reduced drug exposure. There is no data in patients with severe renal or hepatic impairment. The concomitant administration of low dose oral MTX has no effect on the PK of sarilumab, nor does prior biological DMARD treatment. However, exposure of simvastatin (CYP3A4 substrate) decreases by 45% when co administered with a single dose of sarilumab 200 mg. This is consistent with inhibition of

IL-6 signalling resulting in restoration of CYP activity, leading to increased metabolism of drugs that are CYP substrates. The effect of sarilumab on CYP enzymes may be clinically relevant for a CYP substrate. Positive ADA status has a significant impact on the PK of sarilumab resulting in a 24 to 28% lower drug exposure when compared to ADA negative patients and lower still if patients exhibit a persistently positive response to ADA. Sarilumab concentrations of neutralising antibody positive patients appeared to be lower versus neutralising antibody negative patients (by 49 to 59%).

Pharmacodynamics

Sarilumab leads to a rapid and dramatic decrease in serum CRP within 2 to 4 days of first drug administration. The median time to nadir CRP levels is 7 days with a return to near normal 15 to 30 days after last drug administration. Other acute phase reactants such as serum amyloid A (SAA) and fibrinogen levels follow a similar time course of effect. With repeat sarilumab dosing, CRP levels reach steady state by Week 24 and remain at the same level up to Week 52 of therapy. The mean values for free sIL-6R decreased rapidly (2 weeks) following SC administration of sarilumab and remained constant thereafter for at least 24 to 52 weeks.

The effect on free sIL-6R and CRP levels, and efficacy endpoints was apparent only at drug concentrations achieved with doses of 150 mg q2w or above. A plateau was reached for all endpoints at the sarilumab concentration for the 200 mg q2w dose. The Phase II study also showed a greater reduction in neutrophil counts with increasing sarilumab up to 200 mg q2w. The PK/PD analyses supported the conclusion from the dose response relationships that the 150 and 200 mg q2w doses were appropriate for the Phase III program. In the Phase III studies, both 150 and 200 mg q2w doses showed near maximal suppression of serum CRP levels. The combined Phase III trial dataset shows that a higher percentage of patients treated with sarilumab 200 mg q2w had sarilumab trough concentrations above 1 mg/L by Week 24 (86%) than patients treated with sarilumab 150 mg q2w (61%).

The PK/PD relationships for safety endpoints (neutropaenia, elevated serum ALT values and raised LDL levels) showed a higher rate of adverse effects with an increasing sarilumab concentration, but the effect reached a plateau at the lower concentration range observed with sarilumab 150 mg q2w therapy, apart from neutropaenia. There was also a small increased risk of severe neutropaenia ($< 1.0 \times 10^9$/L) occurring in patients at the median concentration for sarilumab 200 mg q2w compared to 150 mg q2w.

Efficacy

The doses selected for the pivotal studies were based on Phase I and II studies with the lowest sarilumab dose regimen of 150 mg q2w and the next regimen of 200 mg q2w chosen along with a lack of dose response relationship for treatment emergent averse events (TEAEs). In addition, for patient convenience, a less frequent injection schedule was selected (q2w versus qw).

Study EFC11072 (Part B)

This is a 52 week, multicentre, multinational, Phase III, randomised, double blind, parallel group, placebo controlled trial in 1,369 adult patients with active rheumatoid arthritis and an inadequate response MTX primarily comparing 150 mg and 200 mg of sarilumab + MTX (up to 25 mg/week) versus placebo + MTX via fortnightly SC injections. Stable doses of corticosteroids and NSAIDs were allowed but DMARDs other than MTX were ceased. There were a large number of exclusion criteria. The study was a continuation of the Phase II, Part A of the study, whose patients did not participate in Part B. Part B originally had 6 arms and 2 cohorts with the first cohort investigating 5 sarilumab dose regimens with MTX and one arm on placebo + MTX. Once the results of Part A were known, that is the 2

doses for further investigation, patients in these arms continued and the other arms exited to the open label, long term extension Study LTS11210. The primary efficacy analysis was based on Cohort 2 of Part B (1,197 patients) who were recruited after dose selection results were available from Part A and were randomly assigned in a ratio of 1:1:1 to receive either placebo injections q2w, sarilumab 150 mg q2w or sarilumab 200 mg q2w. Early escape to rescue therapy at the highest dose of 200 mg q2w was allowed. A number of protocol amendments were made, including allowing a lower MTX dose in some countries, modifying exclusion criteria and conversion of HAQ-DI and mTSS to co-primary endpoints (see Attachment 1) which included EMA and FDA involvement.

For Cohort 2, 16.8% of patients discontinued (mainly due to AEs) and did not take rescue therapy and 21.5% switched to open label rescue therapy (majority were on placebo). Study completion occurred in 68% of sarilumab groups and 49% of the placebo group. 2.9% of subjects had a protocol deviation that could have impacted efficacy. Baseline demographic factors were well balanced (mean 52 years, 82% female, 86% Caucasian, median body mass index (BMI) was 27.3 kg/m2, 19% from Western Europe, North America, Australia and New Zealand) and baseline rheumatoid arthritis disease characteristics were similar indicating severely active rheumatoid arthritis (mean rheumatoid arthritis duration 9 years, 85% rheumatoid factor positive, 87% positive for anti-cyclic citrullinated peptide (anti-CCP) antibodies, 27 tender joints, 17 swollen joints, mean DAS28-CRP score 5.95, mean CRP 22 mg/L, mean mTSS 46 to 55 and mean HAQ-DI 1.64). Median baseline MTX dose was about 15 mg/week, 62 to 67% received systemic corticosteroids and 70 to 72% received NSAIDs. Co-morbid conditions were similar in the 3 groups.

There were 3 co-primary efficacy endpoints with results as follows:

- ACR20 response at Week 24 was 58.0% in the 150 mg group and 66.4% in the 200 mg group versus 33.4% for placebo; p-values < 0.0001 for both sarilumab doses compared with placebo. No treatment interactions by subgroups were seen except for anti-CCP antibody patients.
- HAQ-DI score mean change at Week 16 was -0.54 for the 150 mg group and -0.58 for the 200 mg group versus -0.30 for placebo; p < 0.0001 for both sarilumab doses compared with placebo. No treatment interactions by subgroups were seen except for anti-CCP antibody and RF patients.
- mTSS change at Week 52 showed smaller increases from Baseline were observed in subjects treated with sarilumab (0.90 for the 150 mg group and 0.25 for the 200 mg arm) than in patients treated with placebo (2.78); p < 0.0001 for both sarilumab doses compared with placebo. No treatment interactions by subgroups were seen except for smoking history.

The key secondary efficacy endpoint of major clinical response at Week 52 (ACR70 maintained for ≥ 24 consecutive weeks) was 12.8% in the 150 mg group and 14.8% in the 200 mg arm compared to 3.0% on placebo; p < 0.0001 for both sarilumab doses compared with placebo. The majority of other secondary endpoints were statistically significant.

Study EFC10832

This is a 3 arm, multicentre, multinational, randomised, double blind, parallel group, placebo controlled Phase III trial of 24 weeks duration in 546 patients with active rheumatoid arthritis who were inadequate responders to or intolerant of anti-TNF therapy, comparing sarilumab 150 mg q2w, sarilumab 200 mg q2w or placebo q2w. Protocol amendments occurred including a similar conversion of HAQ-DI to a co-primary endpoint. There were a large number of exclusion criteria. Stable doses of CS and NSAIDs were allowed and concomitant treatment with non-biological DMARD therapy (for example, MTX 10 to 25 mg/week) was required. All patients who completed were eligible

to enter Study LTS11210. Early escape to rescue therapy occurred in 20.9% (higher for placebo patients) and discontinuations from the study and not taking rescue therapy occurred in 13.4% (mainly due to AEs). Study completion overall was 69.1 to 72.3% for sarilumab versus 55.8% for placebo. Baseline demographic factors were well balanced (mean 54 years, 82% female, 71% Caucasian, median BMI 28.2 kg/m2, 43% from Western countries) and baseline rheumatoid arthritis disease characteristics were similar indicating severely active rheumatoid arthritis (mean rheumatoid arthritis duration 12 years, 76% rheumatoid factor positive, 78% positive for anti CCP antibodies, 29 tender joints, 20 swollen joints, mean DAS28-CRP score 6.20, mean CRP 27 mg/L and mean HAQ DI 1.78). Concomitant medications were similar across the groups with 93% taking one concomitant non-biological DMARD (79% MTX), 63% received any corticosteroids and 70% received NSAIDs. The baseline and concomitant mean MTX dose was similar across the treatment groups (median weekly MTX dose of 15 mg in all 3 treatment groups). Co-morbid conditions were similar in the 3 groups.

There were 2 co-primary efficacy endpoints with results as follows:

- ACR20 response at Week 24 was 55.8% in the 150 mg group and 60.9% in the 200 mg group versus 33.7% for placebo; p-values < 0.0001 for both sarilumab doses compared with placebo. No treatment interactions by subgroups were seen except for a higher rate of ACR20 response to placebo therapy was observed in non-Caucasian subjects (49.1%) and geographic Region 2.
- HAQ-DI score mean change at Week 12 -0.50 for the 150 mg group (p = 0.0007) and -−0.49 for the 200 mg arm (p = 0.004) versus -0.29 for placebo. Female subjects showed a higher treatment related mean HAQ-DI response compared to a small effect in males due to a high placebo response.

About half the secondary endpoints were statistically significantly in favour of sarilumab (See Attachment 1) based on the hierarchical testing and most of the remainder were nominally in favour of sarilumab.

Other efficacy studies

The evaluator has discussed a number of other efficacy studies in the clinical evaluation report, as discussed below.

Study EFC11072, Part A

This was a 12 week, 6 arm, dose ranging study intended to select the 2 dose regimens of sarilumab for further evaluation in the Phase III rheumatoid arthritis program and to demonstrate the effectiveness of sarilumab when added to MTX in 306 patients with rheumatoid arthritis. The groups were balanced with respect to demographic features and were similar with respect to baseline rheumatoid arthritis disease characteristics. A statistically higher rate of ACR20 response at Week 12 was demonstrated in the sarilumab 150 mg qw group (72.0%) compared to placebo (46.2%, Hommel adjusted p value = 0.0203). Statistically significant ACR20 responses (after multiplicity adjustment) were not demonstrated in any of the other sarilumab dose groups compared to placebo, although a trend towards treatment effect was seen in the 150 mg q2w, 100 mg qw and 200 mg q2w sarilumab treatment arms.

Study LTS11210

This is an ongoing, open label, long term (up to 5 years) extension study in adult patients with rheumatoid arthritis who completed involvement in 5 earlier trials, with subjects continuing their previous concomitant treatments. The primary objective is to evaluate the long term safety of sarilumab, but persistence of efficacy response is a secondary objective. The main efficacy endpoints are maintenance of clinical response and radiographic progression and the efficacy data presented was for Weeks 24, 48, 96, 114,

192 and 216 and the radiographic data summarises 2 years of data in total (1 year from Part B of Study EFC11072 and 1 year from Study LTS11210). All efficacy analyses are descriptive in nature with no statistical adjustments being performed. Data from 1,910 patients is currently available with most from Study EFC11072 (Part B). 23.0% of enrolled subjects had ceased treatment at the data cut-off point. Between Weeks 24 and 216, the proportion of patients obtaining ACR20 response was 83 to 90%, obtaining ACR50 response was 60 to 70%, obtaining ACR70 response was 39 to 50% and achieving DAS28-CRP remission was 51 to 62%. The rates of ACR response and remission were sustained and stable between Weeks 24 to 216 after an initial increase in clinical response rates between Weeks 0 to 24, which reflects the contribution from patients who initiated sarilumab at Week 0 in Study LTS11210. For X-ray data, 848 patients had 3 sequential X rays collected over 100 weeks. At Week 0 in Study LTS11210 (that is after 1 year of treatment in Study EFC11072), the mean mTSS had increased by 1.05 units relative to the baseline of the initial trial in the combined sarilumab treatment cohort. At Week 100 (after 52 weeks of treatment in Study EFC11072 and 48 weeks of treatment in Study LTS11210), the mean mTSS had increased by 1.34 units from the original baseline. The rate of non-progression at Week 0 of Study LTS11210 (that is Week 52 of Study EFC11072) was 51.9%. There was minimal change between Weeks 0 and 48 of Study LTS11210 for the proportion of subjects showing no X-ray progression at Week 100 (51.2%) versus Week 52 (51.9%).

Study SFY13370

This was a randomised, double blind, double dummy trial which primarily aimed to assess the safety and tolerability of sarilumab and tocilizumab in adult patients with active rheumatoid arthritis who were inadequate responders to or intolerant of anti-TNF drugs. The rates of ACR20, ACR50, ACR70 and DAS28-CRP response at Week 24 were collected as exploratory efficacy outcomes. The proportion of patients achieving an ACR20 response at Week 24 was similar in patients treated with sarilumab (63.3% for the 150 mg q2w group and 68.6% for the 200 mg q2w arm), but lower than that observed for patients treated with tocilizumab (75.5%), however this study was not designed to evaluate comparative efficacy.

Safety

A total of 2,887 patients have received at least one dose of any strength of sarilumab + non-biological DMARD therapy in the Phase II and III rheumatoid arthritis clinical development program with 1,546 patients exposed for > 48 weeks and 624 patients exposed for > 144 weeks. For the requested doses, 1,321 patients have received either the 150 mg or 200 mg doses in the placebo controlled studies and > 600 patients have been exposed for > 6 months. Almost all were exposed to concomitant MTX.

For Part B of Study EFC11072, comparing 150 mg, 200 mg and placebo, treatment emergent adverse events were higher on sarilumab than placebo (74.5%, 78.1% and 61.6%), with infection being the most frequent (40.1%, 39.6% and 31.1%). TEAEs were also higher for sarilumab for blood and lymphatic system disorders (primarily due to neutropaenia (10.7%, 15.8% versus 0.5%), also thrombocytopaenia (1.2%, 1.4% versus 0%)), general disorders and administration site conditions (mostly due to injection site reactions of localised erythema, pruritus and rash) and abnormal investigation results (mainly due to raised serum transaminases (hepatic disorders were 12.3%, 11.8% versus 4.7%) and lipids (3.9%, 4.0% versus 1.9%)). Unexpectedly, 12 cases of depression were reported on sarilumab versus 1 on placebo (10 were non-serious). Study EFC10832 reported a higher rate of TEAEs on sarilumab than placebo with infection again being the most common, including 3 cases of oral herpes, 5 cases of pneumonia and 2 cases of fungal skin infection only seen in sarilumab patients. Comparing 150 mg, 200 mg and placebo, neutropaenia (12.7%, 12.5% versus 1.1%), leukopaenia, thrombocytopaenia, elevation of

serum lipids (11.6%, 8.2% versus 1.7%), injection site reactions (8.8%, 8.2% and 1.1%, especially erythema and pruritus) and elevation of serum transaminases (5.0%, 11.4% versus 1.1%) were all higher on sarilumab than placebo. Other studies are discussed in Attachment 1, including an auto-injector suggesting the incidence and type of AEs were consistent with the known safety profile of sarilumab. Adverse drug reactions were higher on sarilumab than placebo with the profile similar to the TEAEs. No patient in the Phase II or III trials developed reactivation of latent tuberculosis. The overall rate of MACE was 0.6 per 100 PY.

In Part B of Study EFC11072, 5 deaths occurred during the double blind treatment period (2 each in the placebo and sarilumab 150 mg groups and 1 in the sarilumab 200 mg arm) and 2 patients died during the open label, rescue treatment period (1 in the placebo group and the other in the sarilumab 200 mg arm). Two of the sarilumab patients died from cardiovascular events, one died 13 days after surgery for a perforated duodenal ulcer and two had malignancies. Study EFC10832 had one death on placebo. In the long term safety population, the exposure adjusted incidence rate of death with sarilumab + DMARDs is 0.4 deaths per 100 PY. The evaluator considered the rates and causes of death on sarilumab were consistent with what would be expected in an rheumatoid arthritis patient population with underlying co-morbid disease conditions and the rate of death did not increase over time.

In Part B of Study EFC11072, SAEs were higher in the sarilumab treatment groups (8.8% on 150 mg and 11.3% on 200 mg) compared with the placebo group (5.4%) with the most common being infection. One case of osteomyelitis and one case of necrotising fasciitis were reported on sarilumab. One case of gastrointestinal perforation was reported on sarilumab. SAEs of neutropaenia (7 sarilumab versus 0 placebo) and elevated serum transaminases (5 sarilumab versus 0 placebo) were only reported on sarilumab. Study EFC10832 also had a higher incidence of SAEs on sarilumab (3.3% on 150 mg, 5.4% on 200 mg and 3.3% on placebo) mostly due to infection. Neutropaenia and increased serum transaminases as SAEs were also only reported on sarilumab. The rate of SAEs in the long term safety population was slightly higher on the 200 mg regimen than the 150 mg regimen (11.3 SAEs/100 PY versus 9.0 SAEs/100 PY), mainly due to infection, and remained constant over time. Pneumonia was higher on 200 mg but neutropaenia was higher on 150 mg. Two patients on 200 mg had pancytopaenia and 6 patients had pancreatitis (only one considered possibly related).

Discontinuations due to AEs were higher on sarilumab than placebo (for example Part B of Study EFC11072 had 12.5% on 150 mg, 13.9% on 200 mg and 4.7% on placebo) with infections, neutropaenia, thrombocytopaenia and increased serum transaminases being the most frequent reasons. In the long term safety population, the exposure adjusted discontinuation rate did not increase and infection was the most common reason along with neutropaenia and increased serum ALT.

In both pivotal studies, mean increases from Baseline were observed in serum transaminases (ALT and AST) as well as serum total bilirubin for both doses of sarilumab compared with placebo with no clear dose response. The mean values of ALT, AST and total bilirubin remained within the normal range for all 3 treatment groups. However, both doses of sarilumab increased baseline serum ALT by 40 to 45% (versus no change with placebo) and both doses of sarilumab increased serum AST by 25% (versus no change with placebo). ALT > 3 x ULN was more frequent on sarilumab as to was ALT > 5 x ULN (Part B of EFC11072), AST > 3 x ULN and increased bilirubin. Raised serum ALT was 44.5% on sarilumab 150 mg, 53.8% on sarilumab 200 mg and 32.8% on placebo in Part B of EFC11072 and in Study EFC10832 was 27.8% on sarilumab 150 mg, 28.0% on sarilumab 200 mg and 18.2% on placebo. The incidence of abnormal liver function tests was numerically higher in the long term safety population, but the overall pattern of abnormal liver function tests were consistent with that seen in the placebo controlled

populations with the majority of elevations being ALT > 1 to 3 x ULN. The onset of the ALT > 3 x ULN was most prevalent within the first 6 months of administration with no trend of increasing occurrence over time. Six patients recorded serum ALT values > 3 x ULN in conjunction with total serum bilirubin > 2 x ULN but had other explanations for the elevations, that is not Hy's law cases.

A dose dependent decrease in neutrophil cell count was seen on sarilumab with neutropaenia higher on sarilumab than placebo. In Part B of EFC11072, neutropaenia occurred in 10.7% on sarilumab 150 mg, 15.8% on sarilumab 200 mg and 0.5% on placebo with 8 cases all on sarilumab being serious. There was no case of neutropaenia resulting in hospitalisation and about half of all subjects identified with neutropaenia continued with study medication. A similar pattern of neutropaenia was seen in the other pivotal study. Patients with an absolute neutrophil count < 1 x 10^9/L in the controlled population was 5.9% on 200 mg and 4% on 150 mg with no cases reported on placebo. In the longer term safety population, neutropaenia (any grade) was numerically higher (15.5% on sarilumab 150 mg and 19.8% on sarilumab 200 mg). Severe neutropaenia (< 1.0 x 10^9/L) was also numerically higher in patients taking sarilumab 200 mg (9.7%) versus sarilumab 150 mg (5.9%) in the long term safety population.

Thrombocytopaenia also occurred on sarilumab and in Study Part B of EFC11072, there were 9 significant cases (platelet count < 100 x 10^9/L), all on sarilumab, and in Study EFC10832 there were 6 significant cases in the sarilumab 200 mg group versus no subjects in the other 2 treatment groups. In the long term population, thrombocytopaenia was also higher on 200 mg (2.2%) than on 150 mg (0.7%).

Increases in lipids were observed in both pivotal studies with no clear dose response relationship and most being due to raised triglycerides but these were not associated with pancreatitis. In the long term safety population, elevations in lipid parameters remained consistent with what was observed in the placebo controlled populations.

Patients reporting an increase in weight ≥ 5% from Baseline were higher on sarilumab than placebo and the percentage of patients with increased blood pressure changes was higher in the sarilumab groups. Increases in creatinine were slightly higher on sarilumab than placebo. In the long term safety population, no clinically relevant changes were observed for vital signs, including blood pressure and changes from Baseline in subject weight.

Anti-drug antibodies developed more frequently on sarilumab than placebo, for example a positive ADA assay result during the study was 5.9% on placebo, 22.6% on sarilumab 150 mg and 16.0% on sarilumab 200 mg in Study EFC11072 but neutralising antibodies were low (0.2%, 3.5% and 2.4% respectively). Long term, the overall rate of ADA positivity in any sarilumab dose group was 16.3% with 2.0% neutralising. Hypersensitivity reactions were slightly higher on sarilumab than placebo including a patient who developed a reaction on Day 358. No cases of anaphylaxis were reported in the pivotal studies but there were 4 cases of serious hypersensitivity AEs in the long term population.

Subgroup analyses showed patients weighing < 60kg had a higher rate of neutropaenia than those ≥ 60 kg (for example for 150 mg, 14.4% versus 5%). A higher frequency of serious infection was observed in patients on sarilumab whose weight was > 100 kg or receiving weekly MTX dose > 20 mg.

Clinical evaluator's recommendation

The clinical evaluator has recommended approval of Kevzara for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have failed to respond to or are intolerant of 1 or more DMARD drugs (including prior anti-TNF therapy). The evaluator commented on the proposed dosage regimen as follows:

'However, on the balance of scientific evidence, the sponsor proposed posology for sarilumab is insufficiently acceptable. The sponsor proposed posology for sarilumab therapy recommends 200 mg q2w as the regimen for the majority of patients, and the dose of sarilumab can be reduced to 150 mg q2w for the management of neutropaenia, thrombocytopaenia and elevated liver enzyme tests. The clinical evaluator recommended the posology of sarilumab be 150 mg q2w for all patients as the totality of the clinical dataset indicates that this is the lowest, most clinically effective regimen with an acceptable safety profile'.

Risk management plan

The TGA has accepted the EU Risk Management Plan (EU-RMP) for Kevzara (sarilumab), (version 1.0, dated 9 June 2016, data lock point 17 February 2016), with Australian Specific Annex (ASA) (version 2.0, dated 31 August 2016), to be revised to the satisfaction of the TGA, however there were some outstanding matters.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised above in Table 7.

Additional pharmacovigilance activities proposed by the sponsor include a North American Pregnancy registry to monitor risks in the missing information concern of use in pregnant women, a knowledge and understanding survey in HCPs in Europe post-launch to evaluate the effectiveness of risk minimisation measures, paediatric investigational plans (for polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis, proposed in the EU-RMP), a safety surveillance program using existing EU rheumatoid arthritis registries and a knowledge and understanding survey in HCPs and patients post-launch in Australia to evaluate the effectiveness of risk minimisation measures.

Risk minimisation activities proposed by the sponsor include PI, CMI and Package insert: 'Instructions for use' for patients, a health care professional guide to educate prescribers and pharmacists on actions to minimise specific identified risks and a Patient Alert Card.

There were five outstanding recommendations from the RMP evaluator that the sponsor should follow up with the TGA and in the pre-ACPM response:

- The following safety concerns should be added, with consideration given to proposing appropriate pharmacovigilance and risk minimisation activities:
  - Missing information: Use in patients with hepatic impairment
  - Missing information: Use in patients with renal impairment
  - Missing information: Long term use
  - Missing information: Use in patients switching to/from sarilumab
  - Important potential risk: Progressive multifocal leukoencephalopathy
  - Important potential risk: autoimmune disorders including demyelinating disorders
- Advisory committee for the safety of medicines (ACSOM) advised that it would be useful to make reference to the European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis with synthetic and biological DMARDs in the PI (in the HCP guide).
- The 'Summary of the RMP' in the ASA does not assign the additional pharmacovigilance activities (Pregnancy registry, Safety Surveillance program) to the relevant safety concerns. It is recommended that all ongoing pharmacovigilance

activities that contribute to the safety database and have been described in the ASA should be listed against the corresponding safety concern in the ASA.

- Long term safety results from Trial LTS11210 should be submitted, and this study should be assigned as an additional pharmacovigilance activity for the suggested missing information safety concern: 'long term use.'
- Provision of the study plan and questionnaires for the knowledge and understanding surveys, along with the final draft education materials for review prior to launch.

ACSOM commented that information from EU patient registries may be relevant to Australia if the experience of patients is likely to be the same in both Australia and Europe. However differences in climatic conditions and sunlight exposure on rates of non-melanoma skin cancer may not necessarily capture these issues from overseas registries. ACSOM also commented that a disease registry is likely to be the best approach to monitoring SAEs including immunogenicity. The sponsor will be asked to address these issues in the pre-ACPM response and with the RMP evaluator.

Risk-benefit analysis Delegate's considerations

Quality

The quality evaluator has no objections to approval on quality grounds and has recommended batch release testing as a condition of registration. There are outstanding GMP clearances that will need to be provided prior to registration and the issue raised by the FDA is being considered.

Nonclinical

The nonclinical evaluator had no objections to the registration of Kevzara however these is an outstanding issue with regards to pregnancy classification that is discussed below.

Clinical

Efficacy

The pivotal studies demonstrated efficacy of both doses of sarilumab in patients with moderate to severe active rheumatoid arthritis on a background of non-biological DMARDs (mostly MTX) using validated co-primary efficacy endpoints covering signs and symptoms of active rheumatoid arthritis, physical functioning and progression of structural joint damage. The pivotal studies covered 24 to 52 weeks duration with 1,743 patients enrolled and are supported by a Phase II study and a long term extension study in 1,910 patients thus far, demonstrating a maintenance of effect for 2 years. Both of the Phase III trials included patients who had previously been exposed to anti-TNF drugs and also those who were anti-TNF naïve. The submission broadly followed the EU guideline on rheumatoid arthritis and the baseline demographic and disease related characteristics of patients in both of the Phase III trials are similar to those in the anticipated Australian patient cohort. However both studies excluded patients who were at a significant risk of infection (particularly, tuberculosis) or malignancy, or who had various abnormal laboratory results at Baseline (for example abnormal haematology, liver function tests or lipid parameters). In addition, there were many exclusion criteria including a history of inflammatory bowel disease, severe diverticulitis and previous gastrointestinal perforation and study completion was not high at around 70% for sarilumab and about 49 to 56% for placebo, which reduce the generalisability.

The evaluator commented that the dose of MTX used may have been suboptimal in some patients in the clinical studies and that there were some differences in clinical response for patients on MTX < or ≥ 15 mg/week, however the sponsor has responded that these doses are consistent with that reported in the literature for longstanding rheumatoid arthritis, that optimising dose needs to also consider safety and tolerability and the sarilumab responses were maintained. The evaluator also commented that the baseline mTSS scores, which indicate the extent of joint damage, were higher than seen in trials with other biological medicines, for example tocilizumab, suggesting that patients were at high risk of further x-ray progression, in addition to positive serology for autoantibodies. The evaluator was concerned that this could enrich the treatment response and limit the generalisability of the results of Cohort 2/Part B of Study EFC11072 to the majority of patients with rheumatoid arthritis being treated in Australia (in particular, much lower rates and burden of established joint damage with definitive treatment commenced at an earlier stage of the condition). However, the sponsor has responded indicating the scoring system used for tocilizumab was different and that the baseline mTSS in the sarilumab study when adjusted was similar to that used in the Lithe study of tocilizumab and therefore the results are generalisable to the Australian population. The sponsor has provided a response to these issues and others addressing comments by the evaluator and this will be provided to the committee. Overall, the clinical evaluator recommended approval (see below on dose).

Dose

Both pivotal studies compared 2 doses of sarilumab with placebo but were not designed or had pre-specified statistical testing to determine superiority of the higher dose over the lower dose. The sponsor comments that the efficacy data presented in this submission consistently shows a numerical superiority for 200 mg over 150 mg, particularly for the higher levels of ACR response, radiographic outcomes and pharmacological inhibition of IL-6. However the rates of ACR50 and ACR70 response at Weeks 12, 24 and 52 for both doses of sarilumab are numerically similar with overlapping 95% CIs for the treatment related difference (versus placebo) in response rates. Subgroup analyses were supportive of this except for patients treated with 150 mg q2w who weighed ≥ 100 kg had the lowest rate of ACR20 response at 24 weeks (40.0% versus 35.9% for placebo). For patients who decreased their dose due to certain laboratory abnormalities, and noting the limitations of this analysis, the Week 12 and 24 results after having decreased the dose of sarilumab from 200 mg q2w to 150 mg q2w in Study LTS11210 did not show an apparent decrease of effect on ACR20 response rate and mean change from Baseline in HAQ-DI score. A post hoc analysis by the sponsor of pooled data from both pivotal studies suggested a potential benefit from 200 mg dose on ACR20 (64.7%) versus 150 mg (57.3%); difference of 7.4% (95% CI 1.9%, 12.9%). Post hoc analyses of X-ray data by the sponsor were also submitted to support the superiority of the 200 mg dose, however as with all post-hoc analyses, they have limitations in interpreting the results. Although the PD data supported the higher dose, this should not override the clinical efficacy and safety data.

The clinical evaluator comments that 150 mg q2w appears to be the lowest, most clinically effective dosing regimen. The sponsor requested dose of 200 mg q2w has not demonstrated significant superiority for efficacy outcomes over 150 mg q2w and there is a potential for increased adverse events with the higher dose (for example infection (including herpes zoster infection), neutropaenia, and thrombocytopaenia). The sponsor is proposing a reduction of dose from 200 mg to 150 mg for management of neutropaenia, thrombocytopaenia and elevated liver enzymes however the Delegate is minded to agree with the evaluator that the 150 mg q2w dose should be the standard dose for all patients as this is the lowest most clinically effective dose. The ACPMs advice is requested on this matter.

Body weight

An increase in body weight resulted in reduced drug exposure with the impact greater at the extremes of body weight range. A lower rate of ACR20 response at Week 24 was seen for patients weighing ≥ 100 kg treated with sarilumab 150 mg q2w when compared to placebo. However, no consistent effect of high subject weight was seen for the other efficacy endpoints. Subject weight > 100 kg was associated with a higher incidence of overall and infection related AEs. The sponsor should include information on this in the PI.

Safety

The safety profile for sarilumab was demonstrated in 1,220 patients with rheumatoid arthritis in the pivotal studies and about 3,000 patients treated with any dose of sarilumab. Adverse effects include an increased risk of infection, opportunistic infection (mainly oral herpes viral and zoster infection), neutropaenia, thrombocytopaenia, raised hepatic transaminases and serum lipids and injection site reactions. Overall, a higher incidence of AEs, SAEs and AEs resulting in permanent treatment discontinuation were observed in sarilumab treatment groups. The majority of infections were mild-moderate, self-limiting, and were predominately upper respiratory tract infection, urinary tract infection or nasopharyngitis. No patients developed reactivation of latent tuberculosis, however there was an increased risk of oral herpes virus infections with sarilumab. Hypersensitivity reactions were an uncommon type of AE reported at a slightly higher incidence in patients receiving sarilumab compared to placebo. Most hypersensitivity AEs were non-specific reports of rash, which were rated as mild in severity, resolved without specific intervention and did not result in discontinuation.

Neutropaenia is a recognised safety concern with anti-IL-6 therapy and over the long term follow-up period of the Phase III studies, the incidence of neutropaenia was up to 20% however the majority of neutropenic episodes were transient and not associated with infection related AEs. The number of patients with an absolute neutrophil count (ANC) < 1 x 109/L in the controlled population was slightly higher than reported for tocilizumab and this increased in the long term population. Raised liver enzymes and thrombocytopaenia are also of concern. The sponsor is proposing dose reductions to 150 mg for neutropaenia, thrombocytopaenia and raised liver enzymes and laboratory monitoring. GI perforation/ulceration/diverticulitis was slightly higher on sarilumab. The risk of malignancies needs longer follow-up, as to for MACE events. ADA development was low. Unexpectedly there was an increase in cases of depression. Mortality rates were similar between sarilumab and placebo therapy in short term follow-up. Since sarilumab has not been registered overseas yet there are no post-market data.

Pregnancy category

The sponsor has requested Pregnancy Category B2;[16] for sarilumab however the nonclinical evaluator has recommended Category C;[15] consistent with the category for tocilizumab and based on the data available at present. The evaluator and sponsor have both provided information to support different pregnancy categories for sarilumab and an analysis of this is located in the nonclinical evaluation report. There was inconclusive evidence from an embryofetal toxicity study to suggest that sarilumab may cause stillbirths and pregnancy loss in cynomolgus monkeys and it has been observed in other studies (such as tocilizumab's) that there is a trend for slight increases in abortion/embryo-foetal death due to the administration of high doses of an IL-6R inhibitor in non-human primates. The nonclinical evaluator considers Pregnancy Category C as most appropriate owing to its pharmacological effects, may be suspected of causing harmful effects on the human fetus or neonate without causing malformations (the definition of the category includes effects that are reversible). The evaluator also had some uncertainties associated with the reproductive toxicity of sarilumab. The sponsor's response to this matter also included some clinical information from patients who became

pregnant whilst in the sarilumab clinical trial. In the sarilumab plus DMARDs long term safety population, there were 14 patients who became pregnant and 4 male patients whose partner became pregnant (plus one patient on sarilumab monotherapy). Of the 15 patients, five delivered a healthy child, one child had pneumonia at birth, 7 patients had miscarriages (patients were receiving DMARDs or were of older maternal age) and 2 were ongoing. Of the 4 male patients whose partners became pregnant, 2 delivered a healthy child, one was ongoing and one had an elective abortion. Based on the limited data regarding sarilumab use in pregnant women during the clinical trials, the sponsor is recommending that sarilumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab. At this stage with the limited data available, and for consistency with tocilizumab, the Delegate is inclined to support Pregnancy Category C. The ACPM's advice is requested on this matter.

Home based treatment

The pivotal studies in this submission initiated sarilumab in healthcare settings and the first injection was usually performed by a healthcare professional. Just over half of all injections were performed by the patient or caregiver at home. The overall incidence of TEAEs was comparable in the professional and non-professional drug administration groups, as were the most common types of AEs however some injection site reactions were slightly higher in the non-professional administration group (erythema and pruritus) which is unlikely to be clinically significant. The approved PI for tocilizumab specifies that the first injection must be performed under the supervision of a healthcare professional in a healthcare setting able to manage serious immediate hypersensitivity reactions. Although anaphylaxis has not been reported, there were cases of potential systemic hypersensitivity reactions with sarilumab long term. Therefore the Delegate supports the evaluator's recommendation that sarilumab should be initiated in a supervised healthcare setting (as for tocilizumab). The ACPM's advice is requested on this matter.

RMP

An RMP with an ASA has been provided, however there are outstanding matters which the sponsor should address prior to registration. The Delegate supports the RMP evaluator's recommendations.

Overall

The quality, nonclinical and clinical evaluators have recommended approval, and an RMP/ASA has been provided, pending satisfactory resolution of GMP and RMP matters and other issues identified during the evaluation. Pending further advice from the ACPM, satisfactory resolution of the above issues and further consideration of the manufacturing deficiencies raised by the FDA, the Delegate proposes to register Kevzara for the proposed indication.

Data deficiencies

The pivotal studies were not designed or powered to evaluate significant differences between the 2 sarilumab doses. Sarilumab has not been studied in patients < 18 years of age, in subjects with significant organ dysfunction (including renal, hepatic or cardiac failure), those at risk of reactivated latent tuberculosis, in the setting of live vaccines, and in pregnant or lactating women. There is insufficient long term data on potential risks of malignancy (including non-melanoma skin cancers) and major adverse cardiovascular events.

Conditions of registration

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

1. The implementation in Australia of the EU Risk Management Plan for Kevzara (sarilumab), (version 1.0, dated 9 June 2016, data lock point 17 February 2016), with Australian Specific Annex (version 2.0, dated 31 August 2016), to be revised to the satisfaction of the TGA, included with Submission PM-2015-04024-1-3.
2. The following study reports must be submitted to the TGA as soon as possible after completion, for evaluation: as Category 1 submission: Study LTS11210.
3. Batch Release Testing:
    a. It is a condition of registration that all batches of Kevzara/Ilsidex imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
    b. It is a condition of registration that each batch of Kevzara/Ilsidex imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.
4. Compliance with Certified Product Details (CPD): The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in an application or notified through a self-assessable change.

Questions for the sponsor

The sponsor is requested to address the following issues in the pre-ACPM response:

1. Please address the outstanding RMP matters with the RMP evaluator and provide a summary of the sponsor's response to these matters in the pre-ACPM response. In the response include how the sponsor intends to address the advice from ACSOM regarding differences in risk for Australian patients compared to European in regards to climatic conditions and sunlight exposure on rates of non-melanoma skin cancer. Please also discuss if the safety surveillance program using existing EU registries proposed will include monitoring for SAEs, including immunogenicity.
2. Provide an analysis of reports of depression from across the entire safety population.
3. Provide a summary of the issues raised by the FDA in their Complete Response Letter and how they relate to the submission to the TGA.

Response from sponsor

1. Non-melanoma skin cancers: risk difference in European vs Australian Patients

The sponsor notes the ASCOM's observations regarding the differences in climatic conditions and levels of sunlight exposure across Australia and Europe, and whether such differences could contribute to differences in the rates of non-melanoma skin cancer (NMSC). Whilst the incidence of NMSC in the general population varies from country to

country, as noted in Table 8 below, Australia has a much lower aged standardised incidence rate of NMSC compared to the UK and other parts of Europe.[29]

Table 8: Age standardised (world) incidence (per 100,000) and cumulative (0-74) incidence (percent) rates and standard errors

	Male					Female				
	Cases	ASR (W)		CUM 0-74		Cases	ASR (W)		CUM 0-74	
*Sweden	7887	14.3	0.18	1.33	0.03	6325	8.7	0.14	0.84	0.02
Germany, Brandenburg	6292	50.2	0.66	5.70	0.09	5859	36.8	0.54	4.20	0.07
Germany, Bremen	3052	89.7	1.70	10.54	0.23	2822	64.8	1.43	7.57	0.19
Germany, Free State of Saxony	11875	51.7	0.50	5.90	0.07	10974	36.1	0.41	4.15	0.05
Germany, Hamburg	4725	57.7	0.87	6.76	0.13	4665	45.4	0.76	5.39	0.10
Germany, Mecklenburg–Western Pomerania	5074	62.5	0.91	7.45	0.13	5128	49.5	0.78	5.80	0.10
Germany, Munich	99	0.6	0.06	0.06	0.01	98	0.5	0.06	0.04	0.01
Germany, North Rhine–Westphalia	8601	70.2	0.80	8.07	0.11	7731	51.4	0.68	5.82	0.09
Germany, Saarland	3126	57.9	1.09	6.72	0.15	2824	42.8	0.94	4.78	0.12
Germany, Schleswig–Holstein	14041	98.4	0.87	11.57	0.12	13451	78.7	0.78	9.16	0.10
UK, England	169801	73.5	0.19	8.27	0.03	141899	51.2	0.16	5.71	0.02
UK, England, East of England Region	14018	50.5	0.46	5.50	0.07	10811	32.8	0.37	3.58	0.05
UK, England, North Western	25303	87.0	0.58	9.90	0.08	23486	66.4	0.50	7.41	0.07
UK, England, Northern and Yorkshire	26799	87.3	0.57	9.94	0.08	23333	62.9	0.47	7.07	0.06
UK, England, Oxford Region	12241	105.3	1.00	11.74	0.14	10158	75.9	0.84	8.61	0.12
UK, England, South and Western Regions	42441	120.5	0.64	13.72	0.09	34901	84.5	0.53	9.47	0.07
UK, England, Thames	7605	14.0	0.17	1.31	0.02	5222	6.9	0.11	0.66	0.02
UK, England, Trent	13623	95.4	0.87	10.69	0.12	10977	66.8	0.73	7.46	0.10
UK, England, West Midlands	20416	82.1	0.61	9.14	0.09	17020	57.2	0.51	6.33	0.07
UK, Northern Ireland	6462	97.2	1.26	10.95	0.18	5652	65.0	0.97	7.19	0.13
UK, Scotland	21369	94.4	0.68	10.75	0.10	18903	64.6	0.53	7.16	0.07
UK, Wales	16	0.1	0.03	0.01	0.00	26	0.2	0.04	0.02	0.00
Oceania										
Australian Capital Territory										
Australia, New South Wales	26	0.1	0.02	0.01	0.00	26	0.1	0.02	0.01	0.00
Australia, Northern Territory	33	5.6	1.02	0.63	0.15	13	2.4	0.68	0.20	0.06
Australia, Northern Territory: Indigenous	6	6.1	2.66	0.63	0.30	7	5.7	2.28	0.55	0.28
Australia, Northern Territory: Non–Indigenous	26	5.4	1.11	0.63	0.17	6	1.4	0.61	0.10	0.05
Australia, Queensland	298	1.9	0.11	0.18	0.02	176	1.1	0.09	0.12	0.01
South Australia	222	3.4	0.24	0.35	0.03	191	2.1	0.18	0.20	0.02
Australia, Tasmania	83	3.7	0.44	0.40	0.06	52	1.9	0.32	0.19	0.04
Australia, Victoria	260	1.3	0.09	0.13	0.01	230	1.0	0.07	0.09	0.01
Western Australia	227	3.0	0.21	0.30	0.03	148	1.7	0.15	0.15	0.02
New Zealand	200	1.3	0.09	0.12	0.01	186	1.0	0.08	0.09	0.01
New Zealand: Maori	8	0.7	0.27	0.07	0.03	8	0.6	0.23	0.06	0.03
New Zealand: Pacific Islander	2	0.5	0.34	0.05	0.04	1	0.3	0.25	0.04	0.04
New Zealand: Other	190	1.3	0.10	0.12	0.01	177	1.0	0.09	0.09	0.01

In the sarilumab safety population, (NMSC) were observed at a rate of 0.8 per 100 PY in the placebo group and 0.5 per 100 PY in the sarilumab 200 mg group. No NMSC were reported in the 150 mg group.

The NMSC rate of 0.5 per 100 PY observed in the 200 mg sarilumab patient group is consistent with what has been reported in the literature for another IL-6R antagonist, tocilizumab (0.4 per 100 PY).[30]

Importantly, this rate is also consistent with the NMSC rate (0.6/100 PY) reported in a meta-analysis of 74 trials in patients with RA treated with anti-TNF agents.[31]

Given the rates of NMSC are not increased for sarilumab relative to other biologic DMARDs used for rheumatoid arthritis, the sponsor considers that there is no signal from the clinical program that would warrant a specific monitoring of NMSC.

2. Analysis of reports of depression

The sponsor notes the Delegate's request for an analysis of reports of depression in patients in the safety population. In MedDRA, events relating to depression are in the High-Level Group Term (HLGT) Depressed mood disorders and disturbances in the Psychiatric disorders System Organ Class (SOC). There is also a HLGT Suicidal and self-injurious behaviours NEC. The following analyses include events that are in either of these 2 HLGTs (see Table 9).

[29] Forman D, et al. Editors (2013). Cancer Incidence in Five Continents, Vol. X (electronic version). Lyon: International Agency for Research on Cancer.
[30] Rubbert-Roth A, et al. Malignancy rates in patients with rheumatoid arthritis treated with tocilizumab. *RMD Open* 2016;2:e000213. doi:10.1136/rmdopen-2015- 000213.
[31] Askling J, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomised controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiol Drug Saf* 2011; 20: 119–30.

Table 9: Number (%) of patients with TEAE(s) in SOC Psychiatric disorders by selected HLGT and HLT during the entire TEAE period; Placebo-controlled safety population (Pool 1)

		Sarilumab	
	Placebo + DMARD	150 mg q2w + DMARD	200 mg q2w + DMARD
HLGT: High Level Group Term	(N=661)	(N=660)	(N=661)
High Level Term	n (%)	n (%)	n (%)
PSYCHIATRIC DISORDERS	14 (2.1%)	17 (2.6%)	19 (2.9%)
HLGT: Depressed mood disorders and disturbances	2 (0.3%)	9 (1.4%)	9 (1.4%)
HLT: Depressive disorders	2 (0.3%)	8 (1.2%)	7 (1.1%)
Depression	1 (0.2%)	7 (1.1%)	6 (0.9%)
Depression suicidal	0	1 (0.2%)	0
Dysthymic disorder	0	0	1 (0.2%)
Major depression	1 (0.2%)	0	0
HLT: Mood alterations with depressive symptoms	0	1 (0.2%)	2 (0.3%)
Depressed mood	0	1 (0.2%)	2 (0.3%)
HLGT: Suicidal and self-injurious behaviours NEC	1 (0.2%)	1 (0.2%)	1 (0.2%)
HLT: Suicidal and self-injurious behaviour	1 (0.2%)	1 (0.2%)	1 (0.2%)
Completed suicide	1 (0.2%)	0	0
Suicide attempt	0	1 (0.2%)	1 (0.2%)

Source: Appendix 1.4.1.4 ISS. TEAE: Treatment-emergent adverse event.. HLGT: High level group term, HLT: High level term.

In the placebo controlled safety population (Pool 1), a numerically higher incidence of AEs in the HLGT Depressed mood disorders and disturbances for sarilumab treatment groups were observed compared to placebo. No differences in TEAEs between treatment groups were observed for the HLGTs Suicidal and self-injurious disorders.

A medical history of depression was reported for 56 (8.5%) of patients in the placebo group, 33 (5.0%) in the sarilumab 150 mg q2w group and 47 (7.1%) in the sarilumab 200 mg q2w group). A total of 8 patients had both a medical history and TEAE under the HLGT Depressed mood disorders and disturbances; 3 were in the sarilumab 150 mg q2w group and 5 were in the 200 mg q2w group. Patients with history of depression are known to have relapses or exacerbations of depression; however, it is difficult to ascertain the reasons for the higher incidence of TEAE Depression in patients with history of depression in the treated groups.

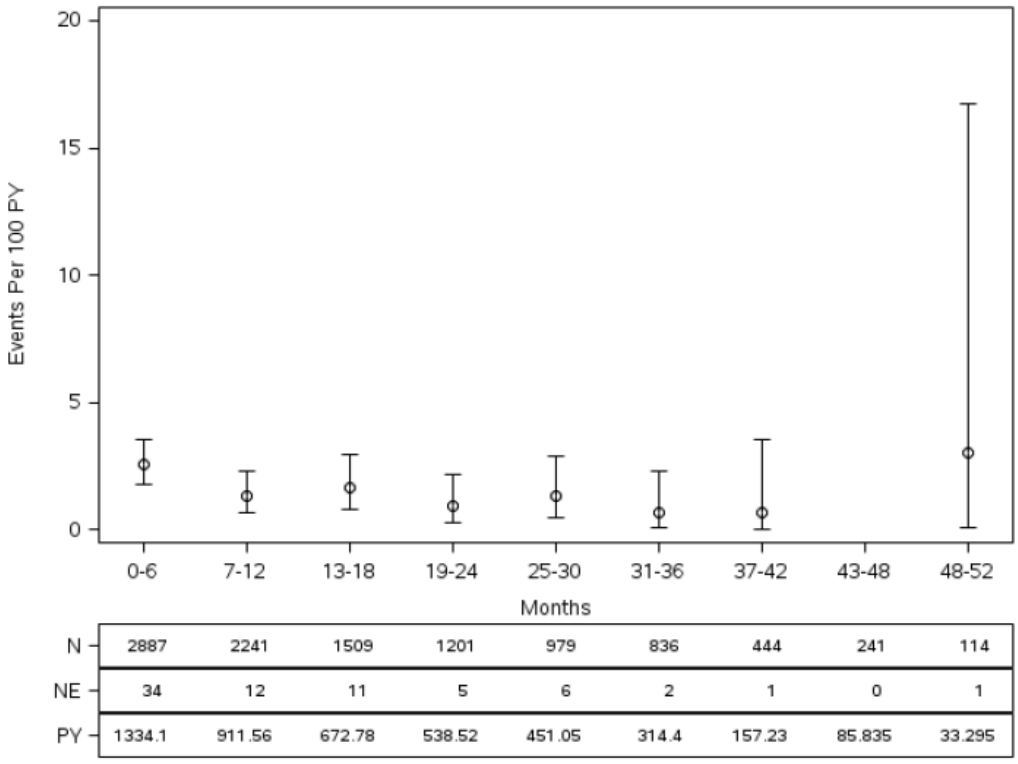
Of the 20 patients with AEs in HLGT Depressed mood disorders and disturbance, 17 patients had non-serious events (1 in the placebo group, 8 in the sarilumab 150 mg q2w group, and 8 in the sarilumab 200 mg q2w group). Of the 3 patients with SAE of depression, 1 was in the sarilumab 150 mg q2w group, and 2 in the sarilumab 200 mg q2w group. Thirteen patients, all in the sarilumab groups, initiated corrective treatment and 9 recovered during the study. The event was assessed to be of mild intensity in 7 patients, moderate intensity in 10 patients, and severe intensity in 1 patient in the sarilumab groups; one event as mild and one moderate in the placebo group. Depression led to permanent withdrawal of treatment in 3 patients, all in the sarilumab groups. Of these 3 patients, 1 ([Information redacted], sarilumab 200 mg q2w group) had an SAE and the other 2 (([Information redacted], sarilumab 200 mg q2w group and ([Information redacted], sarilumab 150 mg q2w group) had non-serious depression. One of the non-

serious depression (verbatim term, worsening of depression with less energy and motivation after investigational medicinal product injection) was assessed to be of severe intensity and related to investigational medicinal product by the investigator, and the other non-serious depression (verbatim term, depressed mood with trigger as significant financial and family stresses) was assessed to be of moderate severity and also related to the investigational medicinal product by the investigator.

There was one report of completed suicide in the placebo group, and one report of suicide attempt in each of the 150 mg and 200 mg sarilumab groups.

In the long term safety population (Pool 2) with sarilumab + DMARDs, the overall event rate for the HLGT Depressed mood disorders and disturbances was 1.6 events/100 PY which is consistent with the event rate observed in the sarilumab + DMARDs treatment group in the placebo controlled population (2.0 events/100 PY in each sarilumab treatment group). In the sarilumab + DMARDs long term safety population, the event rate did not increase over time (see Figure 2, below).

Figure 2: Exposure adjusted event rate in HLGT of Depressed mood disorders and disturbances (95% CI) by 6 month intervals during the entire TEAE and post-study periods; Any sarilumab dose group in the sarilumab + DMARDs long term safety population (Pool 2)



	0-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	48-52
N	2887	2241	1509	1201	979	836	444	241	114
NE	34	12	11	5	6	2	1	0	1
PY	1334.1	911.56	672.78	538.52	451.05	314.4	157.23	85.835	33.295

It is known that depressive symptoms may be difficult to recognise in patients with active rheumatoid arthritis, given the presence of somatic symptoms of depression similar to rheumatoid arthritis including fatigue, sleep difficulties, and appetite fluctuations.[32] Although the incidence and severity of TEAE in HLGT Depressed mood disorders and disturbance of events was numerically higher in the sarilumab treated groups, and the incidence was same for HLGT Suicidal and self-injurious behaviours NEC, and no increase was observed in the event rate over time. As depression is a prevalent condition in the

[32] Iaquinta M and McCrone S. An Integrative Review of Correlates and Predictors of Depression in Patients with Rheumatoid Arthritis. Arch Psy Nur 2015:29 (5):265–278

rheumatoid arthritis population (13 to 20%);[33] this observed difference during the placebo controlled period is not likely due to sarilumab administration.

3. FDA complete response letter

The sponsor provided the details of the response letter as requested which included details relating to the GMP inspection of a manufacturing facility.

4. This section of the sponsor response also included the following information requested by the TGA:

Completion rates and exclusion criteria: generalisability of studies to indicated population: The sponsor believes the results from these pivotal trials are highly generalisable to the indicated population. The eligibility criteria for the pivotal trials were developed based on potential benefit/risk considerations to ensure that the patients participating in these trials had moderate to severe disease activity and to ensure interpretability of the efficacy and safety responses. The baseline demographics and disease characteristics of patients enrolled in these studies were consistent with rheumatoid arthritis patients who had active disease and were generally comparable to those reported for other biological therapies approved for this indicated population.[34,35,36,37,38]

Higher completion rate in the sarilumab arms compared to the placebo arm demonstrated that sarilumab was more efficacious and generally well tolerated in this difficult to treat population of rheumatoid arthritis patients. Moreover, the 2 doses of sarilumab (200 mg q2w and 150 mg q2w) were superior to placebo for the key efficacy parameters, including improvement in signs and symptoms and physical functions and inhibition of progression in radiographic joint damage, that were evaluated in these trials with an acceptable safety profile consistent with this class of therapeutic.

Based on the exclusion criteria from these pivotal studies, for sub-populations where the data for sarilumab was limited or not available, the proposed label has either recommended precaution, such as in patients with hepatic impairment, or has recommended avoidance of administering sarilumab, such as in patients with active infections. Further, the RMP has outlined in detail where there is need for certain exclusion criteria to remain as contraindications, or not, based on the results observed from the sarilumab clinical development program to date. Details for the recommendations and contraindications based on the exclusion criteria are reflected accordingly in the prescriber information and RMP documents.

Further the enrolled patients in these studies had baseline characteristics that are consistent with the requirement of the Australian Government Department of Human Services application for the use of biological treatments of rheumatoid arthritis. Namely,

[33] Cutolo M, et al Burden of disease in treated rheumatoid arthritis patients: going beyond the joint. *Semin Arthritis Rheum*. 2014; 43: 479-488

[34] Emery p, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008; 67: 1516– 1523.

[35] Genovese M, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. *Ann Rheum Dis* 2008; 67: 547–554

[36] Kremer J, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum*. 2011; 63: 609–621

[37] Schiff M, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: The ARRIVE trial. *Ann Rheum Dis*. 2009; 68: 1708–1714.

[38] Weinblatt M, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*. 2003; 48: 35–45

the application requires prior failure of at least 2 or more non-biological DMARDs (prior MTX failure is a key requirement), elevated ESR of greater than 25 mm/hour and/or CRP of greater than 15 mg/L, and at least 20 active swollen and tender joints or 4 major active joints. These requirements to qualify for PBS supply are thus generally comparable to the baseline characteristics of the patients enrolled in the Phase III sarilumab studies. Therefore, the results from these trials are highly relevant and applicable to the Australian rheumatoid arthritis patients who are candidates for biological therapies, such as sarilumab.

Delegate's summary of issues

The primary issues with this submission are as follows with further information in the Discussion section (see above):

1. The sponsor has proposed the standard dose to be 200 mg fortnightly and to be lowered to 150 mg fortnightly for patients with neutropaenia, thrombocytopaenia and elevated liver enzymes. The clinical evaluator supports 150 mg fortnightly for all patients as this is the lowest effective regimen with an acceptable safety profile.
2. The sponsor has requested home based use however there is a potential for hypersensitivity reactions. The sponsor has been requested to include information similar to Actemra in the PI.
3. Sarilumab's safety concerns include, amongst others, an increased risk of infection, injection site reactions, neutropaenia, thrombocytopaenia, raised liver enzymes and hypersensitivity reactions.
4. The sponsor has requested Pregnancy Category B2 for sarilumab however the nonclinical evaluator has recommended Category C, consistent with the category for tocilizumab.

Proposed action

The Delegate had no reason to say, at this time, that the application for Kevzara should not be approved for registration, pending further advice from the ACPM and satisfactory resolution of quality and RMP matters.

Request for ACPM advice

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

1. What are the committee's views on the appropriate dosing regimen for sarilumab?
2. Is the sponsor's proposal for home based use, as described in the 'Dosage' section of the PI, acceptable?
3. Does the committee have any comments regarding the safety profile of sarilumab?
4. What is the appropriate pregnancy category for sarilumab?

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 comments on the issues for which the advice of the ACPM is sought, as described in the Delegate's overview dated 1 November 2016, are provided below. The sponsor is pleased to note the Delegate's proposal to register sarilumab for treatment of rheumatoid arthritis, but respectfully disagrees with the proposed registration of only the

150 mg presentation as use of this dose only is not supported by the extensive safety and efficacy data.

The following information is provided to assist the committee in its discussions on this and other issues raised in the Delegate's overview:

Sarilumab dosing regimen

Sarilumab is a human immunoglobulin IgG1 kappa monoclonal antibody being developed by the sponsor and its business associate for the treatment of rheumatoid arthritis. Sarilumab binds with high affinity to the alpha subunit of the IL-6 receptor (IL-6Rα) and blocks its interaction with interleukin 6 (IL-6), thus preventing IL-6 dependent signal transduction.

Two dose regimens, the 150 mg q2w and 200 mg q2w were selected for the Phase III program. During the Phase III studies both doses had similar ACR20 response rates, however the 200 mg dose provided numerically superior response rates for ACR50 and ACR70, as well as notably larger effects on certain components of the ACR score, specifically pain and physician global assessment. The sponsor acknowledges the Delegate's feedback regarding the lowest effective dose, but reaffirms its position that both doses of sarilumab should be approved.

Prevailing guidelines for the management of rheumatoid arthritis including the most recently revised EULAR guidelines (2013) emphasise the importance of aggressive control of disease and rapid achievement of the therapeutic target in order to minimise irreversible, permanent joint damage and prevent the associated functional disability and loss of productivity. Thus, the sponsor proposed that sarilumab 200 mg q2w was the appropriate the starting dose for the treatment of patients with active rheumatoid arthritis based on the totality of the clinical data, that includes analysis of the data for ACR20 and analysis of the data for median modified total sharp scores (mTSS).

The sponsor remains very concerned that patients will be sub-optimally treated if only the 150 mg is approved in Australia compared with patients in other jurisdictions such as the USA where the 200 mg dose has been recommended for approval by the FDA. The comprehensive data set provided in the registration dossier clearly show that patients who start on the 150 mg dose have poorer joint outcomes at 1 year compared to those who started on 200 mg dose, and never catch up even if they later switch to 200 mg. Given joint destruction is irreversible, as prescribed in the various treatment guidelines, it is essential that the more efficacious dose is available for use from Day 1.

The sponsor believes that the safety profile of the 200 mg is similar to the 150 mg dose with the exception of lab abnormalities. These lab abnormalities, (decreased neutrophils and platelets), have no discernible clinical consequences compared to placebo. Analyses of PD data (CRP) also indicate that suppression of IL-6 signalling was more complete at the end of the dosing interval in patients treated with sarilumab 200 mg q2w.Therefore data indicate that the risk benefit for preservation of joint structure and function strongly favours 200 mg as a starting dose.

Structural joint damage was assessed radiographically in the MOBILITY study and expressed as change in van der Heijde modified mTSS and its components, erosion score, and joint space narrowing scored at Week 52. More patients who received the 200 mg dose had no progression in mTSS (55.6% versus 47.8%; p = 0.0259); in erosion score (62.2% versus 54.8%; p = 0.0341); and in joint space narrowing score (70.4% versus 61.8%; p = 0.0097) over 52 weeks. In contrast, the change from Baseline in mTSS, erosion score, and joint space narrowing score was substantially higher in the sarilumab 150 group indicating greater progression of bone and joint damage than in patients in the 200 mg group. Importantly, these differences were already statistically significant at Week 24.

Post hoc statistical analyses were subsequently performed to explore the differences between doses; In the larger Phase III study, the 200 mg dose was statistically superior to the 150 mg dose at Week 24; 66.4% of patients treated with 200 mg and 58.0% of patients treated with 150 mg (nominal p = 0.0138; the p-value is considered nominal because analyses was post hoc without adjustment for multiplicity) achieved an ACR20 response. In the TARGET study, numerical differences between doses favoured the 200 mg dose but were not statistically significant.

In the MOBILITY study, 64.9% of patients treated with 200 mg versus 54.0% of patients treated with 150 mg had an ACR20 response (nominal p = 0.0017). Significantly more patients achieved higher levels of response by Week 12 when treated with the 200 mg dose than with the 150 mg dose: 36.3% versus 26.5% (nominal p = 0.0024) had an ACR50 response and 17.5% versus 11.0% (nominal p = 00076) had an ACR70 response. The results in the TARGET study were generally similar. Together, the data show that more patients treated with sarilumab 200 mg q2w will achieve treatment goals by 12 weeks of therapy, consistent with the treat-to-target paradigm .To obtain a more precise estimate of difference between the 200 mg and 150 mg doses, data were pooled for Studies EFC11072 and EFC10832. In this analysis, more patients treated with sarilumab 200 mg achieved an ACR20 response at Week 24 (nominal p = 0.0087).

To further quantify the clinical importance of the difference between the 200 mg and 150 mg doses, the sponsor calculated the number needed to treat (NNT) and number needed to harm (NNH) based on the pooled data. In these analyses, the sponsor calculated NNTs for the ACR20 response rate difference between sarilumab 200 mg dose and sarilumab 150 mg dose at Week 24 is 13.5 (95% CI 7.8, 52.6), and rate difference in radiographic non-progression at Week 52 is 12.8 (95% CI: 6.8, 100). In addition, the sponsor calculated NNH for the rate difference between sarilumab doses for serious infection is 90.9 (95% CI 37.0, ∞) based on a rate difference of 1.1% (95% CI -0.6, 2.7) observed in the placebo controlled safety population. The NNH for the rate difference between sarilumab 200 mg and sarilumab 150 mg doses for serious leukopaenia is 200 (95% CI 71.4, ∞) based on a rate difference between the doses of 0.5% (95% CI -0.5, 1.4) observed in the placebo controlled safety population.

In summary, while both doses are superior to placebo, sarilumab 200 mg q2w was superior to sarilumab 150 mg q2w in the prevention of structural progression in rheumatoid arthritis patients. The sponsor considers this is of particular importance in selecting a treatment for rheumatoid arthritis in order to minimise long term destruction of joints. The totality of the data demonstrates that the benefit to risk ratio is favourable for the recommended starting dose regimen of 200 mg q2w for the treatment of patients with active rheumatoid arthritis who had failed prior DMARD/MTX treatment with the possibility to decrease the dose to 150 mg q2w for laboratory abnormalities.

Home based use

The sponsor acknowledges the Delegate's feedback and questions in relating to the first dose and home based use.

Patient eligibility for home based therapy with Kevzara is based on assessment of suitability by the treating medical practitioner, a clear explanation of the risks associated with home use and training of patients and/or their carers on injection technique. Instructions in the proposed PI were included to ensure that patients and/or their carers must receive adequate training on injection technique to enable use in a home setting supported by educational materials for use by the health care provider. The proposed CMI also provides the patient with clear guidance on what they must be aware of and inform their doctor about, before they start using Kevzara at home. This includes seeking immediate medical treatment in the event they experience any symptoms suggestive of a hypersensitivity In accordance with standard medical practice it was intended that the

first dose of Kevzara would be delivered by a healthcare professional in a facility with the necessary medical equipment and treatment protocols to initiate the management of acute hypersensitivity reactions including anaphylaxis. The sponsor has further revised the PI to include the following text that clearly describes the conditions under which the first dose must be administered:

> *'Treatment should be initiated by physicians knowledgeable in the diagnosis and management of rheumatoid arthritis, including experience in initiating treatment with biological therapies.*
>
> *The first dose of Kevzara should be administered initiated under the supervision of a qualified healthcare professional, in a facility with necessary medical equipment, treatments and protocols sufficient to initiate the management of acute hypersensitivity reactions including anaphylaxis are in place'.*

Overall, the information in the PI and CMI together with the supporting educational materials effectively mitigate any potential risks to ensure Kevzara can be safely administered in a home based setting. Considering the chronic nature of rheumatoid arthritis this allows patients and/or carers to avoid taking time away from daily life to receive injections in a health care setting, thus providing significant benefit in quality of life.

Pregnancy category

The sponsor has revised the PI to include Pregnancy Category C to reflect the feedback from the evaluator and Delegate.

Safety profile of sarilumab

The clinical development program to support the use of sarilumab in rheumatoid arthritis is comprised of:

- 9 Phase I studies
- 2 Phase II studies (1 completed study and 1 prematurely terminated study)
- 7 Phase III studies (5 completed studies, 2 ongoing studies and a prematurely terminated Phase III study included in the safety database).

The integrated safety database includes a total of 3,114 patients exposed to at least 1 dose of sarilumab or placebo as the investigational medicinal product, with 95 patients exposed to placebo only and 3,019 patients exposed to sarilumab, providing 4,405.7 patient years of sarilumab exposure.

Of the patients receiving sarilumab, 2,887 patients were on background DMARD therapy and 132 patients have received sarilumab as monotherapy. Of those patients on background DMARD therapy, 1,546 patients were exposed to sarilumab for at least 48 weeks, 1,020 patients were exposed for at least 96 weeks, and 624 patients were exposed for at least 144 weeks.

Safety has been assessed by collecting information on adverse events (AEs), including deaths, other serious adverse events (SAEs); reasons for discontinuation; laboratory tests, and vital signs. There are 3 safety populations in the integrated safety database as follows:

- Placebo controlled population (Pool 1) to compare observations in patients receiving sarilumab + DMARDs with patients receiving placebo + DMARDs;
  - Phase III placebo controlled population (Pool 1a; a subset of Pool 1)
- Sarilumab + DMARD long term safety population (Pool 2) to characterise the long term safety profile and identify uncommon adverse events and events with longer latency periods

- Sarilumab monotherapy population (Pool 3) to assess safety in the absence of concomitant DMARDs.

The safety profile of sarilumab in clinical trials reflected findings observed in nonclinical studies and in clinical studies of the other agent in this class, tocilizumab, based on the anticipated effects of IL-6 inhibition, including an increased risk for infections and changes in laboratory parameters, specifically decrease in absolute neutrophil count (ANC) and increases in hepatic transaminases and in lipids.

The risk of serious infections did not increase over time with long term administration. The most frequent serious infections involved the respiratory tract (that is, pneumonia, bronchitis) and skin and soft tissue (that is, cellulitis, erysipelas). The rate of serious infections, herpes zoster, tuberculosis and other opportunistic infections were similar to rates observed with other biologic therapies used in the rheumatoid arthritis population.

The laboratory changes associated with IL-6 inhibition were decrease in ANC and platelet count and increase in liver function parameters and lipids, and were observed more frequently in sarilumab compared to placebo. These changes in laboratory parameters associated with IL-6 inhibition were effectively managed by dose modification from 200 mg q2w to 150 mg q2w. It should be noted that the sponsor is proposing this same dosage regimen for registration. Importantly, no clinical consequences of the identified laboratory abnormalities were observed. Mean changes in these laboratory parameters, which remained within normal range, generally stabilised after approximately 4 weeks of initiating treatment with sarilumab.

Given changes in laboratory parameters stabilise after approximately 4 weeks of initiating therapy, the proposed laboratory monitoring is to assess ANC, platelet counts, ALT, and lipids within 4 to 8 weeks of initiating therapy and then every 3 months; lipids should be monitored every 6 months. Decreases in ANC did not appear to be associated with an increased risk of infection (including serious infection), decreased platelet counts were not associated with bleeding, elevations in transaminases, and unconjugated bilirubin were not associated with clinically significant hepatic insufficiency, and no cases met Hy's Law criteria (that is, ALT > 3 x ULN and total bilirubin > 2 x ULN with no plausible alternative explanation).

Sarilumab treatment was associated with a higher incidence of hypersensitivity reactions relative to placebo in clinical trials, but these were generally mild and self-limited; the majority were injection site reactions and rashes. Importantly, no cases of severe or serious hypersensitivity or anaphylaxis were reported.

In summary, based on the sarilumab clinical development program, the safety profiles of sarilumab 200 mg q2w and 150 mg q2w doses are acceptable for treatment of patients with moderately to severely active rheumatoid arthritis, in combination with DMARDs. Taking into consideration the efficacy results and overall benefit-risk profile of sarilumab, the clinical trials data support initiation at a dose of 200 mg q2w with dose reduction to 150 mg q2w for management of IL-6 associated laboratory abnormalities (that is, decrease in ANC or platelet count or increase in ALT). The safety data from the global safety database included studies that were also directly generalisable to the proposed patient group, that is patients with moderately to severely active disease who had an inadequate response or intolerance to one or more DMARDs.

Closing remarks

Given the consistent and durable efficacy demonstrated by associated reduction in the signs and symptoms of rheumatoid arthritis, improvement in physical function, and the radiologic evidence for up to 2 years of inhibition of otherwise progressive and irreversible joint destruction, the sponsor is proposing that sarilumab 200 mg q2w be recommended for patients with rheumatoid arthritis who have had an inadequate

response or intolerance to one or more DMARDs. Sarilumab 150 mg q2w showed similarly significant superiority to placebo in the primary efficacy analyses and in the secondary efficacy parameters, although smaller magnitudes of effect were generally observed than with the higher dose regimen. In particular, patients treated with sarilumab 150 mg q2w had more progression of joint damage despite being switched to sarilumab 200 mg q2w. Taken together, these data suggest that sarilumab therapy should be initiated at the higher dose to prevent long term disability associated with joint damage.

Overall the safety profile supports a positive benefit-risk assessment to support approval of sarilumab in combination with non-biologic DMARDs for the treatment of moderate to severe rheumatoid arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs, and the sponsor requests further consideration of approval of both the 200 mg and 150 mg dose.

Advisory committee considerations (ACPM Meeting 313)

The Advisory Committee on Prescription Medicines (ACPM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Kevzara/Ilsidex, solution for injection (prefilled syringes), containing 150 mg and 200 mg of sarilumab, to have an overall positive benefit–risk profile for the indication;

> *'Kevzara in combination with non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) is indicated for the treatment of moderate to severe Rheumatoid Arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs'.*

In making this recommendation the ACPM noted that although the evidence presented showed slightly more efficacy with 200 mg treatment there was also a slightly higher adverse event rate.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration, particularly on the need for satisfactory resolution of outstanding quality and GMP issues and advised on the inclusion of the following:

- subject to satisfactory implementation of the RMP most recently negotiated by the TGA; and
- negotiation of PI and CMI to the satisfaction of the TGA.

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

The ACPM agreed with the Delegate to proposed amendments to the PI and CMI.

Specific advice

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

1. What are the committee's views on the appropriate dosing regimen for sarilumab?

The ACPM agreed with the Delegate that the recommended starting dose should be 150 mg fortnightly, which can be increased if there is an inadequate response and there are no significant safety issues. The view of the committee is that a prescriber would be better to increase the dose if needed rather than decrease a dose because of necessity.

The ACPM noted that 3 monthly reviews of treatment were standard practice, should adjustments to dosing be required.

2. *Is the sponsor's proposal for home based use, as described in the 'Dosage' section of the PI, acceptable?*

The ACPM agreed the sponsor's proposals for home based use were adequate with the proviso that the first injection should be given in a supervised healthcare setting able to manage serious immediate hypersensitivity reactions and with suitable training provided to the patient or carer. The instructions for use document should be provided to the patient.

The ACPM noted the sponsor has agreed to this provision.

3. *Does the committee have any comments regarding the safety profile of sarilumab?*

The ACPM advised that the safety profile was acceptable but appropriate monitoring had to be instigated by the prescriber. Screening should be in line with the standards for other IL-6 inhibitors (for example tuberculosis, hepatitis B, history of diverticulitis etcetera). Sarilumab use should also be in line with the EULAR consensus statement on IL-6 inhibition.

4. *What is the appropriate pregnancy category for sarilumab?*

The ACPM observed that all patients in the reported trials were also on MTX treatment and the PI for that therapy cautions patients should be on adequate contraception. It is therefore unlikely sufficient data on sarilumab safety and efficacy have been collected to warrant anything but a Pregnancy Category C designation.

The ACPM noted that the sponsor has revised the PI advice to Pregnancy Category C.

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.

Post ACPM negotiations

The Delegate agreed that the sponsor could provide additional data to enable resolution of issues of the dose of sarilumab, that is, 150 mg versus 200 mg. The Delegate noted that internationally it appears to be moving towards 200 mg, however the clinical evaluator and the ACPM recommended the starting dose being 150 mg.

The sponsor agreed to provide:

- the updated CSR for the long term safety Study LTS11210 which is now out to 3 years;
- updated summary of clinical safety as provided in the EU submission; and
- the published manuscript for the monotherapy study comparing sarilumab versus adalimumab.

to support the overall benefit risk assessment of the 200 mg starting dose.

Delegate's overview for the second Advisory committee meeting (ACM meeting 2[39]) (2 March 2017)

Background

This is a submission to register a new biological medicine, sarilumab, for the treatment of rheumatoid arthritis in adult patients. The proposed dose is 200 mg every 2 weeks by SC

[39] The name of the committee changed during the time of this submission, the initial presentation was to Advisory Committee for Prescription Medicines (ACPM) at Meeting (number) 313 and the second presentation was to the Meeting 2 of the Advisory Committee for Medicines (ACM).

injection, reduced to 150 mg every 2 weeks if neutropaenia, thrombocytopaenia, or elevated liver enzymes develop.

The clinical evaluator recommended approval of sarilumab, but recommended that the initial dose of sarilumab be 150 mg every 2 weeks for all patients, on the basis of lack of demonstrated superiority of the higher dose, along with a potential for increased adverse events (infection, neutropaenia, thrombocytopaenia). Both the Delegate and the ACPM (Meeting 313, December 2016) supported this recommendation.

Following the ACPM meeting, the sponsor held a teleconference with the Delegate to discuss the issue of appropriate starting dose for sarilumab, and subsequently submitted further data (radiographic data in support of efficacy; and safety data, including a comparison with adalimumab) to support the use of 200 mg as a starting dose.

Also following the ACPM meeting, on 12 January 2017, Health Canada issued a final approval for sarilumab, with a recommended starting dose of 200 mg.

Sarilumab has been submitted, but not approved, in Europe and the US. Approval by the FDA has been delayed due to GMP concerns.

Clinical

Efficacy

Two pivotal studies (Study EFC11072, a 52 week, double blind, placebo controlled study in 1,369 adults with active rheumatoid arthritis inadequately controlled by MTX; and Study EFC10832, a 24 week, placebo controlled study in 546 adults with active rheumatoid arthritis with inadequate response or poor tolerance to TNF therapy) compared sarilumab 150 mg, sarilumab 200 mg, and placebo. These two studies were included in the original submission and previously seen by the ACPM. Primary efficacy outcomes were as follows (p value for comparison with placebo was < 0.0001 for all outcomes except where indicated) as shown in Tables 10 and 11.

Table 10: Primary efficacy outcomes for Study EFC11072

endpoint	sarilumab 150	sarilumab 200	placebo
ACR20 (24 weeks)	58.0%	66.4%	33.4%
HAQ-DI (16 weeks)	-0.54	-0.58	-0.30
mTSS (52 weeks)	+0.90	+0.25	+2.78

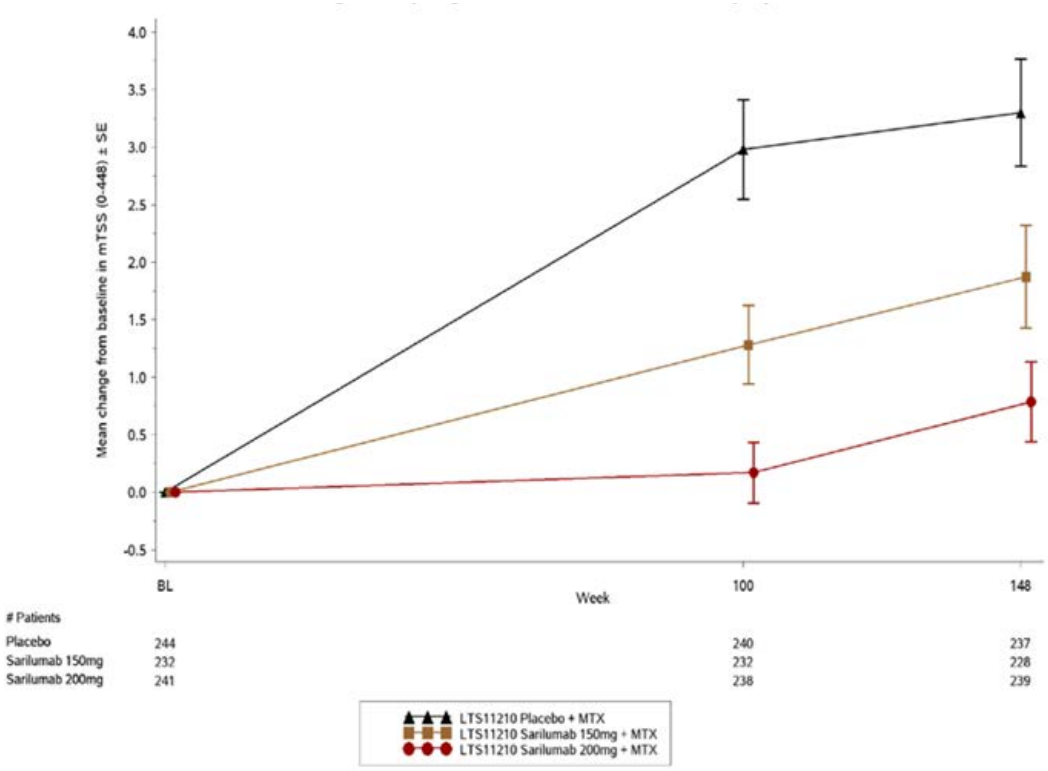
Table 11: Primary efficacy outcomes for Study EFC10832

endpoint	sarilumab 150	sarilumab 200	placebo
ACR20 (24 weeks)	55.8%	60.9%	33.7%
HAQ-DI (12 weeks)	-0.50 (p=0.0007)	-0.49 (p=0.004)	-0.29

Comment: Each dose of sarilumab was statistically superior to placebo for each primary efficacy outcome. Neither study was powered to detect a difference between the two sarilumab dose regimens.

New data [provided] consists of radiographic data relating to patients from Study EFC11072 who were subsequently enrolled in extension Study LTS11210. Patients were up-titrated to (or maintained on) sarilumab 200 mg q2w at the start of the extension study. At the time of the original submission, data to 100 weeks (52 weeks in Study EFC11072, followed by 48 weeks in Study LTS11210) was available; the sponsor has now submitted data to 148 weeks. Results are shown in Figure 3, below.

Figure 3: Figure of mean change from Baseline in the modified total Sharp score (mTSS) at each visit; Study LTS11210 (ITT population)



Comment: Results from the extension study show a significant radiographic benefit for patients initiated on sarilumab 200 mg, which was maintained out to 148 weeks of study, compared to either sarilumab 150 mg or placebo. The numerical difference is however small (the minimum clinically important difference for mTSS is generally stated to be 5 units).

Safety

The clinical evaluator expressed concerns around a potential higher rate of adverse events with the higher dose of sarilumab. In particular, there was a higher rate of neutropaenia with sarilumab 200 mg in Study EFC11072 (see Table 12, below).

Table 12: Rate of laboratory parameter adverse events Study EFC11072

adverse event	sarilumab 150	sarilumab 200	placebo
infection	40.1%	39.6%	31.1%
neutropenia	10.7%	15.8%	0.5%
thrombocytopenia	1.2%	1.4%	0%
ALT increased	44.5%	53.8%	32.8%

Table 13: Rate of laboratory parameter adverse events Study EFC10832

adverse event	sarilumab 150	sarilumab 200	placebo
neutropenia	12.7%	12.5%	1.1%
ALT increased	27.8%	28.0%	18.2%

Comment: Despite the higher rate of neutropaenia seen with sarilumab 200 mg in Study EFC11072, the rate of infection was similar between the two sarilumab dosage regimens.

The sponsor has submitted data relating to the degree of neutropaenia seen with both sarilumab doses across the efficacy program (Table 14).

Table 14: Pooled results from placebo controlled safety population

absolute neutrophil count	sarilumab 150 (N=660)	sarilumab 200 (N=661)	placebo (N=661)
>=1.5x10^9/L to LLN	13.5%	16.3%	3.6%
1-1.5	12.4%	15.0%	1.1%
0.5-1	4.8%	8.4%	0.2%
<0.5	1.2%	0.9%	0.0%

Comment: Intermediate levels of neutropaenia were more common with the higher dose, sarilumab 200 mg, than with sarilumab 150 mg. The highest levels of neutropaenia (< 0.5 x 10^9/L) were not more common with sarilumab 200 mg, but this may reflect the small number of patients who experienced this degree of neutropaenia.

The sponsor has additionally referred to safety results from Study EFC14092;[40] a 24 week randomised double blind study comparing sarilumab 200 mg with adalimumab 40 mg every 2 weeks in 369 patients with moderate to severe rheumatoid arthritis for whom treatment with MTX was inappropriate (see Table 15, below).

Table 15: Safety results from Study EFC14092

adverse event	adalimumab (N=184)	sarilumab (N=184)
absolute neutrophil count:		
>=1.5x10^9/L to LLN	11.5%	23.9%
1-1.5	2.7%	16.8%
0.5-1	1.1%	8.7%
<0.5	0	1.6%
Infections	27.7%	28.8%
- serious infection	2 (bacterial arthritis; URTI)	2 (mastitis; infective bursitis)
- opportunistic infection	1 (pulmonary tuberculosis)	1 (herpes zoster)

Comment: Despite the greater degree of neutropaenia seen with sarilumab compared to adalimumab, the infection rate is similar between the 2 treatment groups.

Discussion

Although the two pivotal studies were not powered to detect an efficacy difference between the two sarilumab dosage regimens, the higher dose was numerically superior for all primary endpoints. An efficacy benefit for sarilumab 200 mg in terms of radiographic outcome was seen in the long term extension study, although the real clinical benefit of the difference may be marginal. The higher dose of sarilumab is associated with a greater degree of neutropaenia; however this is not reflected in a higher incidence of infection in studies up to 52 weeks duration. Additionally, although sarilumab was associated with a markedly increased incidence of neutropaenia compared to adalimumab in a direct head-to-head study, this was again not associated with an increased rate of infection.

Following review of further efficacy data from the extension Study LTS11210, it is recommended that approval be granted for sarilumab for the proposed indication and initial dosage regimen (200 mg every other week). Other requests outlined in the

[40] Burmester GR, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group Phase III trial *Ann Rheum Dis* 2016 ;0:1–8. doi:10.1136/annrheumdis-2016-210310

Delegate's request for ACPM advice are supported. The advice of ACM is sought on this matter.

Delegate's considerations

Although the two pivotal studies were not powered to detect an efficacy difference between the 2 sarilumab dosage regimens, the higher dose was numerically superior for all primary endpoints. An efficacy benefit for sarilumab 200 mg in terms of radiographic outcome was seen in the long term extension study, although the real clinical benefit of the difference may be marginal. The higher dose of sarilumab is associated with a greater degree of neutropaenia; however this is not reflected in a higher incidence of infection in studies up to 52 weeks duration. Additionally, although sarilumab was associated with a markedly increased incidence of neutropaenia compared to adalimumab in a direct head-to-head study, this was again not associated with an increased rate of infection.

Proposed action

Following review of further efficacy data from the extension Study LTS11210, it is recommended that approval be granted for sarilumab for the proposed indication and initial dosage regimen (200 mg every other week).

Request for ACM advice

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

1. What are the committee's views on the appropriate dosing regimen for sarilumab?

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.

Sponsor's response to Delegates request for ACM advice (ACM 2; 2 March 2017)

The committee's advice was previously sought on the proposed registration and starting dose of sarilumab at Meeting 313 (held December 2016). The sponsor was pleased to note the committee's endorsement of registration for sarilumab for the treatment of rheumatoid arthritis, but also noted that the committee had reservations about the proposed 200 mg q2w starting dose and instead recommended approval of the lower 150 mg q2w starting dose with the option to increase the dose to 200 mg if clinically appropriate. Taking into consideration this advice, the Delegate subsequently determined that the benefit-risk assessment supported approval of a fortnightly 150 mg starting dose of sarilumab, with the option to increase the dose to 200 mg if clinically appropriate.

On 31 January 2017, the sponsor submitted additional 12 months data from the ongoing sarilumab long term extension Study LTS11210 which further support the positive benefit/risk profile of the 200 mg starting dose. This was supplemented with a summary of the results from a recently completed study comparing the safety and efficacy of the sarilumab 200 mg q2w dose to another well characterised biologic (adalimumab) in a monotherapy setting.

Following TGA review of this additional long term data, the Delegate's overview (dated 2 March 2017) supported the favourable benefit/risk profile of the 200 mg q2w starting dose. The sponsor fully concurs with this recommendation by the Delegate which aligns with the dosing regimen approved by Health Canada in January 2017. Similarly, no objections to a 200 mg starting dose have been raised by the US FDA or as part of the ongoing evaluation under the centralised procedure in the EU.

The following information is provided to assist the committee in its discussions regarding the 200 mg starting dose.

Benefit-risk considerations to justify the 200 mg starting dose

Guidelines for the management of rheumatoid arthritis including the most recently revised EULAR guidelines (dated 2013) emphasise the importance of aggressive control of disease, and rapid achievement of the therapeutic target in order to minimise irreversible, permanent joint damage and prevent the associated functional disability and loss of productivity.

Two dose regimens, the 150 mg q2w and 200 mg q2w were selected for the Phase III rheumatoid arthritis program. Sarilumab 200 mg q2w was identified by the sponsor as the optimal dose for the treatment of rheumatoid arthritis because of its superior efficacy in the clinically important outcome of inhibiting irreversible joint destruction. The 150 mg dose, while efficacious, does not provide the same level of inhibition of the rate of structural progression. While sarilumab 200 mg has more rapid onset of action and consistently favourable effects on signs, symptoms, quality of life, and inflammatory activity relative to the 150 mg dose, it was the need to prevent long term joint damage that was the basis for the dose recommendation. The sponsor considers that the long term benefit of inhibition of irreversible joint damage demonstrated by sarilumab 200 mg q2w outweighed the short term risk for decreased neutrophil counts, which are transient and manageable with dose modification.

Additional safety and efficacy data collected since the original submission and submitted to the TGA on 31 January 2017 provides additional support for the 200 mg q2w as the starting dose. Evaluation of an additional year of radiographic data, which extended the follow-up period from 2 to 3 years in patients participating in the long term safety Study LTS11210, demonstrated that patients initially treated with sarilumab 150 mg q2w who subsequently received sarilumab 200 mg q2w did not achieve the same levels of inhibition of structural damage as patients who started on 200 mg q2w and continued on this dose (see Figure 3, shown above). Assessment of the additional safety data confirmed that the safety profile remained unchanged.

Additional safety data from other studies ongoing at the time of the original submission, including the safety data from the monotherapy (MONARCH) study, also demonstrate that treatment with sarilumab 200 mg q2w did not lead to any new or increased safety signals compared to the safety data from the original submission. In addition, the safety data from the MONARCH study shows that the incidences of TEAEs, SAEs, and TEAEs leading to treatment discontinuation were generally similar in patients treated with sarilumab and patients treated with adalimumab (Humira), an established biologic for the treatment of rheumatoid arthritis. Differences in the safety profiles of sarilumab and adalimumab were primarily due to the known laboratory changes associated with IL-6 inhibition. Specifically, the incidence of patients with decreased ANC was higher in the sarilumab group than in the adalimumab group; however, the rate of infections, including serious and opportunistic infections, was similar in the 2 dose groups. The safety profile of sarilumab 200 mg q2w dose administered as monotherapy in this study was also comparable to that when administered in combination with DMARDs.

The sponsor does acknowledge the concerns originally expressed by the clinical evaluator, the committee and the Delegate with respect to the potential clinical consequences of decreased neutrophil counts observed in patients participating in the pivotal studies. Evidence provided in the registration dossier, supplemented with additional safety data indicate that long term benefit of inhibition of reversible joint damage demonstrated by sarilumab 200 mg q2w outweighs the short term risk for decreased ANC which is easily monitored, transient and manageable with dose modification, and not associated with increased risk of infection. As noted in the current Delegate's overview dated 2 March 2017, the rate of infection was similar between the 2 sarilumab dosage regimens in the Phase III studies.

Importantly, the risk of serious infections did not increase over time with long term administration. The rate of serious infections, herpes zoster, tuberculosis and other opportunistic infections were similar to rates observed with other biologic therapies used in the rheumatoid arthritis population.

The sponsor's proposed dosing regimen is enhanced by a robust monitoring schedule for ANC specified in the product information with initial assessment recommended 4 to 8 weeks after initiation of therapy, and further assessment every 3 months thereafter. This is more conservative than the corresponding monitoring regimen adopted in the later time points of the long term safety study whereby patients were assessed on a 6 monthly basis. To further enhance the appropriate use of this product, the sponsor has also provided clear guidance in the proposed PI on interrupting and when to recommence therapy based on ANC value.

Ongoing routine pharmacovigilance activities to ensure potential risks are effectively monitored and risk mitigation recommendations will also be implemented. The sponsor considers that the recommended monitoring regimen and dose reduction recommendations in the proposed prescribing information can mitigate the risks associated with ANC reduction in patients being treated with the proposed 200 mg q2w starting dose sarilumab.

Summary

The comprehensive data set provided in the registration dossier demonstrated that patients who initiated treatment with the 200 mg q2w regimen earlier continued to have better radiologic outcomes than patients who initiated treatment with the 150 mg q2w regimen at all time points evaluated up to and including Year 3, and further reinforces the importance of selecting the right start starting dose to minimise further and permanent joint destruction. Additional safety data from studies ongoing at the time of the original submission, including the safety data from the MONARCH study, demonstrates that treatment with sarilumab 200 mg q2w did not lead to any new or increased safety risk compared to the safety data from the original submission. The totality of the submitted clinical data demonstrate a favourable benefit/risk ratio for the recommended starting dose regimen of 200 mg q2w for the treatment of patients with active rheumatoid arthritis, who had failed prior DMARD/MTX treatment with the possibility to decrease the dose to 150 mg q2w for laboratory abnormalities.

Given the irreversible nature of joint destruction, and taking into consideration the consistent and durable efficacy demonstrated by associated reduction in signs and symptoms of rheumatoid arthritis, improvement in physical function and radiologic evidence for up to 3 years, the sponsor is requesting approval of initiation at a dose of 200 mg q2w. Dose reduction to 150 mg q2w remains an appropriate option for management of IL-6 associated laboratory abnormalities (that is, decrease in ANC or platelet count or increase in ALT).

Advisory committee considerations (ACM 2)

The Delegate seeks specific advice on the dosing regimen for sarilumab following its consideration at the previous ACPM meeting in December 2016.

The ACM taking into account the submitted evidence of efficacy, safety and quality, advised that the appropriate starting dose for sarilumab should be 150 mg with an option of increasing to 200 mg as clinically appropriate for the indication:

> *'Kevzara in combination with non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) is indicated for the treatment of moderate to severe Rheumatoid Arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs'.*

In making this recommendation the ACM noted:

- there were 2 pivotal studies in subjects with rheumatoid arthritis that compared sarilumab 150 mg, sarilumab 200 mg (Study EFC11072, Part B; and Study EFC10832) and placebo;
- that available data do not confirm greater efficacy for the higher dose (200 mg) although a trend is evident; and
- that the evidence provided demonstrates a concern for higher toxicity associated with the 200 mg dose. It is likely that in an appropriately powered study the 200 mg dose would be shown to be superior in efficacy to the 150 mg dose but these data were not available. (The higher dose may however be found to have a greater risk of infection and other adverse effects).

Specific advice

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

1. What are the committee's views on the appropriate dosing regimen for sarilumab?

The ACM advised that there was no statistical evidence that the 200 mg dose of sarilumab is superior to the 150 mg for the routine outcome measures such as ACR20 response; but both doses are effective and a trend was seen for greater efficacy with the 200 mg. The ACM noted that the 200 mg dose may inhibit structural damage more effectively than the 150 mg dose in data collected at 3 years. ACM also noted that neutropaenia in one of the pivotal studies was more common in the patients receiving the 200 mg dose and was not seen in the other pivotal study. Furthermore the ACM noted that Health Canada has approved the 200 mg dose but the reason(s) for their support are not clear.

The ACM considered the signal for depression associated with the use of sarilumab, and recommended that depression be added to the RMP as an 'important potential risk' for further analysis in PSURs.

The ACM concluded that the evidence provided in the sponsor's submission supported a starting dose for sarilumab of 150 mg with an option of increasing to 200 mg of sarilumab as clinically appropriate.

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

Post ACM negotiations

The Delegate considered the committee's advice and the sponsor's pre-ACM response and proposed to approve the submission. The Delegate's proposed action is provided the issues raised by ACM, and those by the Delegate below were satisfactorily addressed. To facilitate the finalisation of this submission, the Delegate requested the sponsor to provide updated PI and CMI documents for the product within 10 working days or earlier if possible, incorporating amendments including the following statement on dosage. The recommendations below refer to the annotated PI provided in the sponsor's pre-ACM response.

Summary of requests from the Delegate to the sponsor

EU SmPC

If there is a proposed EU SmPC for sarilumab that has been negotiated with the EMA, could you please submit a copy to the TGA.[27]

Changes to the Product Information

Dosage:[41]

The Delegate has accepted the advice of the committee in regards to the dosing instructions and requests that the sponsor amend the dosing instructions in line with their recommendations. The Delegate has considered the sponsor's pre-ACM response but considers that a starting dose of 150 mg fortnightly, which can be increased as clinically appropriate, to be appropriate given the submitted data. This is broadly consistent with the advice of the clinical evaluator and the ACM (ACPM) on both occasions. Further consideration regarding the dosage can be made once additional data are available for evaluation.

RMP

The Delegate considered the ACM advice regarding depression and agrees that it should be included as an important potential risk in the RMP with further analysis in the PSURs. Please outline the proposed pharmacovigilance activities to address this potential risk, for example investigations from your overseas registry, etcetera. Your analysis in the PSURs should consider potential mechanisms, whether there are potential differences between drugs that bind to IL-6 receptor and IL-6 and the potential role of the receptor for ciliary neurotrophic factor. Please update the RMP/ASA and submit a revised version to the RMP section.

Conditions of registration

The Delegate proposed to include the following specific conditions of registration:

1. Batch release testing

   The Delegate sought clarification from the quality evaluator regarding batch release testing and they have advised that the current wording for batch release testing (number of batches) is standard for all biological medicines and the number of batches required will be determined post approval following further discussions between the biochemistry section and the sponsor. The Delegate recommended that the sponsor follow this up with the biochemistry section post-approval.

2. The implementation in Australia of the EU Risk Management Plan for Kevzara (sarilumab), (version 1.0, dated 9 June 2016, data lock point 17 February 2016), with Australian Specific Annex (version 3.0, dated 14 November 2016), and the responses in the Pre-ACPM Response dated 15 November 2016, to be revised to the satisfaction of the TGA, included with Submission PM-2015-04024-1-3.

   (Note: To be updated following agreement with the RMP evaluator).

3. The following study report must be submitted to the TGA as soon as possible after completion, for evaluation: Study LTS11210.

Summary

The Delegate requested a response to the request within 10 working days (request sent on 24 April 2017).

Outcome

The submission was withdrawn by the sponsor on 26 April 2017. The application in Australia was withdrawn by the sponsor in consideration of the inability to submit

[41] Note only the section regarding Dosage has been included in the AusPAR.

additional efficacy data as part of the review process to further support the 200 mg dosing regimen.

Attachment 1. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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