Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Risankizumab

Proprietary Product Name: Skyrizi

Sponsor: AbbVie Pty Ltd

January 2020

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
%CV	Coefficient of variation
ADA	Adalimumab
ADA/ADA	Subjects who were randomised to adalimumab and re-randomised with adalimumab at the entry of Part B of Study M16-010
ADA/RZB	Subjects who were randomised to adalimumab and switched to risankizumab at the entry of Part B of Study M16-010
ADA/RZB	Subjects who were switched from adalimumab to risankizumab 150 mg in Study M16-010 or Study M15-997
AE	Adverse event(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BSA	Body surface area
C_{avg}	Average plasma concentration
CI	Confidence interval
CMI	Consumer Medicines Information
CNS	Central nervous system
CSR	Clinical study report
DLP	Data lock point
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency (EU)
EU	European Union
Fc	Fragment crystallisable
Fcγ	Fragment crystallisable gamma

Abbreviation	Meaning
GLP	Good Laboratory Practice
HADS	Hospital Anxiety and Depression Scale
HAQ-DI	Health Assessment Questionnaire Disability Index
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin G1
IL	Interleukin
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intention to Treat
IV	Intravenous
K_D	Dissociation constant
KLH	Keyhole limpet haemocyanin
MACE	Major adverse cardiovascular event(s)
MI	Myocardial infarction
MTX	Methotrexate
NAb	Neutralising antibody
NK	Natural killer
NOAEL	No-observed-adverse-effect-level
OLE	Open label extension
PASI	Psoriasis Area and Severity Index
PASI 75	75% reduction in the Psoriasis Activity and Severity Index
PASI 90	90% reduction in the Psoriasis Activity and Severity Index
PBO	Placebo

Abbreviation	Meaning
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
pM	Picomolar
PopPK	Population pharmacokinetic(s)
PsA	Psoriatic arthritis
PSS	Psoriasis Symptom Scale
PUVA	Psoralen and ultraviolet A therapy
PY	Patient years
Q12W	Every 12 weeks
Q16W	Every 16 weeks
Q8W	Every 8 weeks
QoL	Quality of life
RMP	Risk management plan
RZB	Risankizumab
SAE	Serious adverse event(s)
SAP	Statistical analysis plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics (EU)
SOC	System Organ Class
sPGA	Static Physician Global Assessment
STAT3	Signal transducer and activator of transcription 3
t½	Elimination half-life in plasma
Th17	T helper 17
T_{max}	Time of maximum plasma concentration
TNF	Tumour necrosis factor
URTI	Upper respiratory tract infections

Abbreviation	Meaning
UST	Ustekinumab
UTI	Urinary tract infection
γδT cells	Gammadelta T cells

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	15 July 2019
Date of entry onto ARTG:	16 July 2019
ARTG number:	304226
▼ *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Risankizumab
Product name:	Skyrizi
Sponsor's name and address:	Abbvie Pty Ltd Locked Bag 5029 Botany, NSW, 1455
Dose form:	Solution for injection
Strength:	75 mg/0.83 mL
Container:	Prefilled syringe
Pack size:	2
Approved therapeutic use:	*Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults (18 years or older) who are candidates for phototherapy or systemic therapy.*
Route of administration:	Subcutaneous
Dosage:	The recommended dose is 150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. For further information refer to the Product Information.

Product background

This AusPAR describes the application by Abbvie Pty Ltd (the sponsor) to register Skyrizi (risankizumab) for the following indication:

> *[...] treatment of moderate to severe plaque psoriasis in adults.*

Psoriasis is a chronic debilitating immunologic disease characterised by marked inflammation and thickening of the epidermis that result in thick, scaly plaques involving the skin. In most developed countries, prevalence is between 1.5 and 5%.[1] Psoriasis may be classified according to morphologic and clinical presentation; plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, generalised pustular and localised pustular psoriasis, and inverse or intertriginous psoriasis.

Plaque psoriasis is the most common form, affecting approximately 80% to 90% of patients.[2] In patients with plaque psoriasis, approximately 80% have mild to moderate disease, with 20% having moderate to severe disease. Nails of hands and feet are often involved. Nail psoriasis, which has an estimate prevalence of 50% in patients with plaque psoriasis, presents a spectrum of challenges to patients, including pain associated with nail bed hyperkeratosis, functional deficits caused by nail plate crumbling and onycholysis, and cosmetic disfigurement, leading to poor self-image and social stigmatisation.[3] Psoriatic arthritis (PsA) occurs in 30% or more of patients with psoriasis and involves joint pain and destruction, and patients with PsA have reduced quality of life (QoL) and functional capacity compared with psoriasis patients or healthy controls.[4]

Topical corticosteroids are commonly used for mild to moderate cases. Other topical medications include keratolytic agents, anthralin, coal tar, vitamin D analogues, and retinoids. For more widespread disease, phototherapy (ultraviolet B or psoralen with ultraviolet A (PUVA)) is commonly used. Systemic therapy including methotrexate (MTX), cyclosporin, synthetic retinoids, and fumaric acid are often effective in patients with moderate or severe disease. Due to potential adverse side effects of systemic agents, these medications are generally administered in rotation to avoid long term or cumulative toxicities. Biologics have emerged as a promising alternative treatment option for patients with psoriasis. Initial approvals often specified their use only when other systemic agents failed or were contraindicated, but increasingly, approvals and use have reflected that for the moderate to severe plaque psoriasis population, biologics with appropriate risk/benefit profiles can be used on a par with other systemic therapies.[5]

Expression of tumour necrosis factor (TNF)-induced proteins in psoriatic plaques provided the rational for the development of TNF-neutralising therapies for psoriasis, and the anti-TNF agents etanercept, adalimumab and infliximab are approved for the treatment of moderate to severe psoriasis.

Other newer agents, for example, ustekinumab (a potent p40 interleukin (IL) 12/23 inhibitor) is approved for the treatment of moderate to severe psoriasis. While the clinical efficacy of ustekinumab indicates a role for both IL-12 and IL-23 in the pathogenesis of

[1] World Health Organization (WHO). Global Report on Psoriasis. 2016. Available from: the WHO Institutional Repository for Information Sharing (IRIS). Accessed on 15 September 2017.
[2] Menter, A. et al. (2008). Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008; 58 :826-850.
[3] deJong, E.M. et al. (1996). Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. *Dermatology*. 1996; 193: 300-303.
[4] Gladman, D.D. et al. (2005). Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005; 64: ii 14-17.
[5] Menter, A. et al. (2011), American Academy of Dermatology Work Group. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol*. 2011; 65: 137-174.

psoriasis, more recent data suggests that IL-23 is disproportionately involved in the maintenance of chronic psoriasis. IL-23 is thought to be involved in the pathophysiology of psoriasis via induction and maintenance of T helper 17 (Th17) type cells, including type 17 T cells and other IL-23 responsive cells. Other newer agents including ixekizumab and secukinumab which target IL-17 have recently been approved.

While anti-TNF agents have long provided an important therapeutic option for patients with moderate to severe plaque psoriasis, and newer entrants such as IL-17 and IL-12/23 inhibitors have added incremental clinical benefit, the proportions of subjects who achieve at least a 75% reduction in the Psoriasis Activity and Severity Index (PASI 75) (approximately 82% with some agents) leaves many patients without adequate improvement. In addition, lower proportions of patients experience greater improvement (PASI 90), and response rates decrease over time, which leads to patients changing to another medication and the need for more available therapies.[6]

Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that is directed against IL-23 subunit p19. Binding of risankizumab to IL-23 p19 inhibits the action of IL-23 to induce and sustain Th17 type cells, innate lymphoid cells, gammadelta T cells (γδT cells), and natural killer (NK) cells responsible for tissue inflammation, destruction and aberrant tissue repair.

Regulatory status

Skyrizi (risankizumab) is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in the European Union (EU; approved on 30 April 2019), the United States of America (USA; approved on 23 April 2019), Canada (approved on 17 April 2019) and Switzerland (approved on 18 April 2019), and was under consideration in New Zealand (see Table 1).

Table 1: International regulatory status of Skyrizi (risankizumab) as of 15 May 2019

Region	Submission date	Status	Indication
EU (Centralised Procedure)	26 April 2018	Approved 30 April 2019	*Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.*
USA	24 April 2018	Approved 23 April 2019	*Skyrizi is indicated for the treatment of moderate- to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.*
Canada	1 May 2018	Approved 17 April 2019	*Skyrizi is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*
Switzerland	26 April 2018	Approved 18 April	*Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who have had an inadequate response to other systemic therapies*

[6] The Psoriasis Area and Severity Index (PASI) score is a tool used to measure the severity and extent of psoriasis. PASI scores are also used in clinical trials to measure response to treatment (that is, measure treatment efficacy and outcomes), and may be presented as a percentage response rate; for example a PASI 75 response rate represent the percentage of subjects recording a 75% or more reduction in PASI score from Baseline. PASI 100 indicates patients who have achieved a complete resolution of all disease.

Region	Submission date	Status	Indication
		2019	*such as cyclosporine, methotrexate (MTX) or PUVA (psoralen and UV-A) or have contraindications or are intolerant to such therapies.*
New Zealand	25 June 2018	Under evaluation	Under evaluation

Product Information

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

II. Registration timeline

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

Table 2: Timeline for Submission PM-2018-01889-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	2 July 2018
First round evaluation completed	28 November 2018
Sponsor provides responses on questions raised in first round evaluation	1 February 2019
Second round evaluation completed	15 March 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	10 May 2019
Sponsor's pre-Advisory Committee response	15 May 2019
Advisory Committee meeting	7 June 2019
Registration decision (Outcome)	15 July 2019
Completion of administrative activities and registration on the ARTG	16 July 2019
Number of working days from submission dossier acceptance to registration decision*	217

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

Quality

Skyrizi (risankizumab) is a humanised IgG1 monoclonal antibody that selectively binds with high affinity to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor complex. Risankizumab is composed of two heterodimers. Each of the heterodimers is composed of a heavy and a light polypeptide chain. Each heavy chain (γ HC) is composed of 449 amino acids and each light chain (κ LC) contains 214 amino acids. The framework of the risankizumab antibody has been engineered with 2 mutations in the fragment crystallisable (Fc) region to reduce fragment crystallisable gamma (Fcγ) receptor and complement binding.

The following was summarised from the quality evaluation:

- Risankizumab is produced in a mammalian cell line using recombinant DNA technology.
- The sponsor has submitted an application to register the following strength and presentation of risankizumab: 75 mg risankizumab in 0.83 mL solution in prefilled syringe.
- The recommended dose is 150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, 4, and every 12 weeks thereafter.
- There are no objections to the registration of this product from sterility, endotoxin, container safety and viral safety related aspects.
- Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Skyrizi have been controlled to an acceptable level.
- All quality issues have been satisfactorily resolved. There is no objection to the registration of Skyrizi on quality grounds.

Nonclinical

The following was summarised in the nonclinical evaluation:

- The submitted nonclinical dossier was in accordance with the relevant International Conference on Harmonisation (ICH) guideline.[7] The overall quality of the nonclinical studies was generally high. All safety-related studies were Good Laboratory Practice (GLP) compliant.
- Risankizumab has high affinity for human IL-23 (dissociation constant (K_D) ≤ 29 picomolar (pM)). Affinity for cynomolgus monkey IL-23 was also high (K_D < 1 pM). No binding of risankizumab was observed to rat IL-23 and only limited affinity to mouse IL-23 was observed (K_D =15 nM). Risankizumab inhibited human IL-23 mediated signal transducer and activator of transcription 3 (STAT3) phosphorylation *in vitro* with an half maximal inhibitory concentration (IC_{50}) of 24 pM, and inhibited the production of the pro-inflammatory cytokine, IL-17, with IC_{50} values of 2.1 to 7.3 pM for different human IL-23 forms (recombinant and endogenous) and 16.3 pM for

[7] European Medicines Agency (EMA), Committee for medicinal products for human use (CHMP), ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals, EMA/CHMP/ICH/731268/1998, June 2011.

cynomolgus monkey IL-23. *In vivo*, risankizumab inhibited human IL-23 induced skin inflammation in mice, and inhibited the production of cytokines IL-17 and IL-22 in ear tissue.

- Risankizumab staining was observed in extracellular granular material in the placenta consistent with the observation of IL-23 expression in several placental tissue elements, including decidual cells, cytotrophoblasts, and syncytiotrophoblasts reported in the literature.
- Safety pharmacology parameters were assessed in the Good Laboratory Practice (GLP) repeat dose toxicity studies and were found to be unremarkable. No notable changes to central nervous system (CNS; neurological, behaviour and body temperature), electrocardiographic (heart rate, QT interval duration and corrected QT interval duration);[8] or respiratory parameters were reported.
- In monkeys risankizumab showed slow systemic distribution (time of maximum plasma concentration (T_{max}) approximately 2 days), a long elimination half-life (t½) of 7 days and high bioavailability when administered by the clinical route (subcutaneous (SC)). Serum levels were dose proportional. Human pharmacokinetic (PK) parameters were similar to those noted in cynomolgus monkeys (T_{max} approximately 3 to 14 days; t½ approximately 29 days), showing slow clearance (0.31 L/day) with steady state attained by Week 16 of dosing under the clinical regimen (Week 0 and 4 and every 12 weeks (Q12W) thereafter). The PK studies showed that the monkey is an appropriate animal model for toxicity testing.
- Risankizumab had a low order of acute oral toxicity in monkeys.
- Two repeat dose toxicity studies (risankizumab 5 and 50 mg/kg/week) by the clinical route (SC, 4 and 26 weeks) were conducted in monkeys. No treatment-related adverse effects at doses up to 50 mg/kg/week (70 times the clinical area under the concentration-time curve (AUC)) were observed.
- No genotoxicity or carcinogenicity studies were conducted, which is acceptable for a biotechnology–derived pharmaceutical.[7]
- A pre/postnatal development study reported no adverse effects on maternal health, no effect to length of gestation, infant morphometric measurements, neurobehavioural parameters, heart rate assessments, humoral responses to keyhole limpet haemocyanin (KLH) antigen and lymphocyte subset populations at exposure levels 99 times the clinical AUC. The overall incidences of fetal and infant loss were comparable to historical control data.
- Risankizumab was found to cross the placenta (infant:maternal serum ratio 0.17 to 0.86) in monkeys. Risankizumab had no effect on sperm parameters and showed no histological changes to reproductive tissues in male and female monkeys (no-observed-adverse-effect-level (NOAEL) 50 mg/kg/week).

Conclusions and recommendation:

- The submitted nonclinical data were in general accordance with the relevant ICH guideline.[7] All pivotal repeat-dose toxicity and reproductive toxicity studies were GLP-compliant.
- Primary pharmacology studies provided sufficient evidence of risankizumab affinity and selectivity for human and monkey IL-23, as well as neutralisation of its actions.

[8] The QT interval is measured as the time taken from the start of the Q wave to the end of the T wave in the cardiac cycle on an ECG, and represents the time taken from the start of cardiac ventricular contraction to the end of ventricular relaxation. The corrected QT interval (QTc) is the measurement of the QT interval corrected for heart rate.

- Risankizumab was well tolerated, with no treatment-related adverse effects observed in repeat-dose SC studies in monkeys for up to 26 weeks.
- Pregnancy Category B1 is considered appropriate.[9]
- Overall, there are no nonclinical objections to the registration of risankizumab (Skyrizi).

Clinical

The clinical dossier consisted of:

- 3 clinical pharmacology studies providing PK, pharmacodynamic (PD) and safety pharmacology data;
- 3 population PK (popPK) and exposure-response analyses;
- 4 pivotal efficacy/safety studies;
- 1 other efficacy/safety study;
- Other reports; immunogenicity report, major adverse cardiovascular events (MACE) adjudication report (tables), Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) tables, Statistical Analysis Plan (SAP);
- Literature references.

Pharmacology

Pharmacokinetics

Overall, the PK of risankizumab was well studied and characterised. It is based on one study (Study M16-513) in normal volunteers, two PK studies in patients with psoriasis (Studies 1311.1 and M16-007) and five efficacy studies measuring trough levels.

Study M16-513 was conducted in healthy Caucasian, Chinese and Japanese subjects at single escalating doses ranging from 200 to 1200 mg intravenously (IV) and 18 to 300 mg SC. Study 1311.1 was conducted in subjects with moderate to severe plaque psoriasis at doses ranging from 0.01 to 5 mg/kg IV and 0.25 to 1 mg/kg SC. The PK of risankizumab was linear with dose proportional increase in exposure across the evaluated dose ranges of 18 to 300 mg or 0.25 to 1 mg/kg SC, and 200 to 1200 mg or 0.01 to 5 mg/kg IV, and no time dependent kinetics were observed.

Following SC administration of risankizumab, T_{max} was between 3 and 14 days after dosing with absolute bioavailability estimated to be 89% based on cross study population PK analyses. With the clinical dosing regimen of 150 mg SC at Weeks 0, 4, and Q12W thereafter, risankizumab steady state exposure was approximately achieved by Week 16 with estimated steady state peak and trough plasma concentrations of approximately 12 and 2 µg/mL, respectively.

Based on popPK analyses, risankizumab systemic clearance, volume of distribution at steady state, and terminal phase elimination $t_{1/2}$ were estimated to be 0.31 L/day, 11.2 L, and 28 days, respectively, for a typical 90 kg subject. The inter-individual variability (coefficient of variation (%CV)) for risankizumab clearance and central volume of distribution were 24% and 34%, respectively.

[9] Australian Pregnancy Category B1: 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 have not shown evidence of an increased occurrence of fetal damage.

Subjects with body weight > 100 kg were estimated to have approximately 30% lower risankizumab exposure than subjects with body weight ≤ 100 kg but it showed no impact on risankizumab efficacy as assessed by the PASI 90 and Static Physician Global Assessment (sPGA);[10] of clear or almost clear response in the efficacy studies.

Pharmacodynamics

The PD of risankizumab is based on a single PD study in patients with psoriasis who received a single dose of risankizumab and popPK/PD analysis of exposure response.

The single study (Study 1311.1) demonstrated in patients that the inhibition of IL-23 binding to its receptor and subsequent downstream signalling, resulted in decrease in the transciptomic (genes associated with the IL-23/IL-17 axis) and protein (β-defensin 2) biomarkers associated with IL-23/IL-17 axis in patients with moderate to severe compared to placebo.

The popPK/PD analysis conducted on the initial studies (Studies 1311.1 and 1311.2, popPK/PD Report 17/0775) used an indirect response modelling approach followed by simulations for different regimens to establish the dose selection for the pivotal efficacy studies. Simulations across different doses indicated that 150 mg SC dose of risankizumab administered at Week 0, Week 4, and Q12W thereafter would achieve the plateau for efficacy with minimal increase (< 5%) in PASI 90 or PASI 100 at doses higher than 150 mg. Alternative dosing intervals were also evaluated in the simulations, indicating that compared to Q12W dosing, a longer dose interval (once every 16 weeks (Q16W)) would lead to lower efficacy and a shorter dose interval (Q8W) would not result in a meaningful improvement in efficacy.

In addition to the indirect response modelling used in the initial PK/PD analysis, the second popPK/PD analysis (Report 17/0883) evaluated using quartile plots in which subjects were binned into quartiles based on risankizumab average plasma concentration (C_{avg}) levels. The analyses indicated that while the percentage of subjects achieving PASI 90 or sPGA of clear or almost clear responses at Week 16 appeared to have plateaued at the third quartile of risankizumab exposure (median C_{avg} of 3.97 μg/mL), the highest quartile of exposure (median C_{avg} of 7.88 μg/mL) clearly showed a higher percentage of subjects achieving the complete clearance of PASI score (PASI 100). The median Week 0 to 16 C_{avg} value with the proposed clinical dosing regimen (150 mg SC at Week 0, Week 4, and Q12W thereafter) was 7.32 μg/mL, which is similar to the median risankizumab C_{avg} value in the fourth exposure quartile in Study 1311.2.

The data from the popPK/PD analyses confirmed the dose and regimen used in the pivotal efficacy studies.

Dose selection

The recommended dose and dosing regimen used in the pivotal efficacy studies were selected based on safety, efficacy and PK data from the Phase I (Study 1311.1) and Phase II (Study 1311.2) studies in adult patients with plaque psoriasis, and on formulation considerations, patient acceptability considerations, as well as exposure response analyses. The dose selected for the Phase III program reflected advice received from regulatory authorities at the end of Phase II.

The proposed dose and dosing regimen of 150 mg SC (given as two 75 mg injections) at Week 0, Week 4, and then subsequently Q12W is well supported by the dose finding studies and popPK/PD analyses submitted in the application.

[10] The Static Physician Global Assessment (sPGA) is a doctor's global assessment of a subject's psoriasis based on severity of induration, scaling, and erythema. The sPGA is a scale from 0 to 5; a score of 0 indicates clear and a score of 5 indicates severe disease.

Efficacy

Pivotal studies

Studies M15-995 (UltIMMa-2) and M16-008 (UltIMMA-1)

Studies M15-995 and M16-008 were identical Phase III, multicentre, multinational, randomised, double blind, double dummy, placebo and active comparator controlled, parallel design study compared risankizumab to ustekinumab and placebo in subjects with moderate to severe chronic plaque psoriasis (see Figure 1). Patients eligible for enrolment were ≥ 18 years with diagnosis of moderate to severe chronic plaque psoriasis (with or without PsA) for at least 6 months (defined as involved body surface area (BSA) ≥ 10% and a PASI score ≥ 12 and a sPGA score of ≥ 3) and must be a candidate for systemic therapy or phototherapy for psoriasis treatment. Drug induced or non-plaque forms of psoriasis, active inflammatory diseases and PsA, known chronic or acute infections were excluded (Table 3).

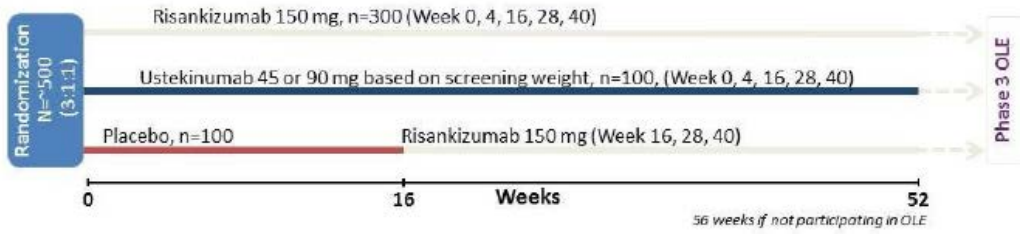
Objectives

The main objectives of both studies were to assess the efficacy and safety of risankizumab, compared to ustekinumab and placebo in subjects with moderate to severe chronic plaque psoriasis. In addition, both assessed PK and the emergence of anti-drug antibodies and their effect on efficacy and safety.

The co-primary efficacy endpoints were evaluated at Week 16. Additional endpoints were evaluated at Week 52. Approximately 500 subjects with moderate to severe chronic plaque psoriasis were planned for this study. Subjects who failed screening were not re-screened. The screening period ranged from 1 to 6 weeks, followed by a 16 week treatment period (Part A). Patients were randomised into a 3:1:1 (risankizumab, ustekinumab and placebo).

At Week 16, all subjects initially randomized to placebo began receiving 150 mg risankizumab. Subjects were to continue to receive treatment through Week 40 and were to be followed through at least 52 weeks (Part B). Subjects could then either end their study participation or enter the open label extension study (Study M15-997) provided they met eligibility criteria and desired to continue treatment. Subjects not wishing to continue in the open label study were to have a final visit at 56 weeks.

Figure 1: Study Design for Studies M15-995 (UltIMMa-2) and M16-008 (UltIMMA-1)



OLE = open-label extension

Table 3: Restricted medication for Studies M15-995 (UltIMMa-2) and M16-008 (UltIMMA-1)

Medication or class of medications	Restriction duration (through EOO Visit)
guselkumab, tildrakizumab	not allowed neither before nor during trial participation
briakinumab, secukinumab (Cosentyx®),	6 months prior to randomization
brodalumab, ixekizumab	4 months prior to randomization
adalimumab (Humira®), infliximab (Remicade®) investigational products for psoriasis (non biologics)	12 weeks prior to randomization
etanercept (Enbrel®) live virus vaccinations	6 weeks prior to randomization
any investigational device or product (excludes psoriasis products) other systemic immunomodulating treatments (e.g. methotrexate, cyclosporine A, corticosteroids[1], cyclophosphamide) , tofacitinib (Xeljanz®), apremilast (Otezla®) other systemic psoriasis treatments (e.g. retinoids, fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g., PUVA).	30 days prior to randomization
phototherapy (e.g., UVA, UVB) topical treatment for psoriasis or any other skin condition (e.g. corticosteroids[2], vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, α-hydroxy, fruit acids)	14 days prior to randomization

[1] No restriction on corticosteroids with only a topical effect (e.g. inhalative corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).
[2] Exception: Topical steroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to trial visit in which PASI is assessed.

The primary efficacy outcomes (comparing risankizumab with placebo) were:

- Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16;
- Achievement of sPGA score of clear or almost clear at Week 16.

The Delegate has noticed discrepancy in the secondary endpoints mentioned in the study synopsis and protocol which needs to be clarified by the sponsor.[11]

The ranked secondary outcomes are as follows:

- Ranked secondary outcomes:

1. Risankizumab is not different from placebo with respect to achieving sPGA of clear at Week 16.
2. Risankizumab is not different from placebo with respect to PASI 100 response at Week 16.
3. Risankizumab is not different from placebo with respect to achieving a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16.[12]

[11] The sponsor clarified that each clinical study report (CSR) synopsis reflects the final SAP, which included additional ranked secondary endpoints and adjusted the ranked order of the endpoints that were included in the study protocols. The SAPs for all the pivotal studies were finalised before the unblinding of treatment for any study.
[12] The Dermatology Life Quality index (DLQI) is a dermatology specific 10 item patient-answered questionnaire designed to assess the impact of skin disease on health related quality of life as a patient reported outcome. Total DLQI scores range from 0 to 30 with lower scores indicating better quality of life outcomes. A score of 0/1 is interpreted as having no effect on patient's life.

4. Risankizumab is not different from placebo with respect to achieving a Psoriasis Symptoms Scale (PSS) score of 0 at Week 16.
5. Risankizumab is not different from ustekinumab with respect to PASI 90 response at Week 16.
6. Risankizumab is not different from ustekinumab with respect to achieving an sPGA of clear or almost clear at Week 16.
7. Risankizumab is not different from ustekinumab with respect to PASI 100 response at Week 16.
8. Risankizumab is not different from ustekinumab with respect to achieving an sPGA of clear at Week 16.
9. Risankizumab is not different from ustekinumab with respect to PASI 90 response at Week 52.
10. Risankizumab is not different from ustekinumab with respect to PASI 100 response at Week 52.
11. Risankizumab is not different from ustekinumab with respect to achieving an sPGA of clear at Week 52.
12. Risankizumab is not different from ustekinumab with respect to PASI 75 response at Week 12.
13. Risankizumab is not different from ustekinumab with respect to achieving an sPGA.
14. Risankizumab is not different from ustekinumab with respect to achieving a DLQI score of 0 or 1 at Week 16.
15. Risankizumab is not different from placebo with respect to mean change from baseline in PSS total score at Week 16.

Further endpoints (summarised) included various other PASI responses (50, 75 90 and 100 at all visits); and time to loss of PASI 75, 90, 100, and sPGA 0-1.

Exploratory endpoints on biomarkers were also assessed.

Results

Overall, baseline demographics were similar between the treatment arms within each study. There were more males than females in the study. The majority of patients were Caucasian.

Baseline mean scores on PASI and BSA and the distribution of sPGA scores were balanced between the treatment groups. Approximately 10% of subjects in each group had a diagnosis of PsA, and another approximately 20% in each group had suspected PsA. The treatment groups were balanced with regard to prior psoriasis medication history.

Exposure was comparable between treatment groups during Part A and Part B. The mean exposure was similar between treatment arms however Study M16-008 had a slight longer cumulative duration of risankizumab.

Co-primary endpoint

The co-primary endpoints (Part A) were achieved in each study. Statistically significantly larger proportions of subjects in the risankizumab groups achieved both PASI 90 and sPGA clear or almost clear at Week 16 compared with the placebo groups (Table 4).

Table 4: Studies M15-995 and M16-008 Analysis results of primary endpoints, non-response imputation (Intention to Treat populations)

	Study M15-995			Study M16-008		
	Placebo	Risankizumab		Placebo	Risankizumab	
Endpoint	n/N (%)	n/N (%)	*P*-value[a]	n/N (%)	n/N (%)	*P*-value[a]
PASI 90 at Week 16	2/98 (2.0)	220/294 (74.8)	< 0.001	5/102 (4.9)	229/304 (75.3)	< 0.001
sPGA clear or almost clear at Week 16	5/98 (5.1)	246/294 (83.7)	< 0.001	8/102 (7.8)	267/304 (87.8)	< 0.001

NRI = non-responder imputation

a. Across the strata, *P*-value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

Treatment effects in all pre-specified subgroups were in favour of risankizumab with 95% confidence interval of the treatment difference excluding zero in every subgroup in each study (Study M15-995 and Study M16-008).

The sensitivity analyses of the primary endpoints including the 11 subjects from Site [Information redacted] who were excluded from the efficacy analysis also yielded similar results (Study M15995).

Ranked secondary endpoints

Risankizumab treatment was compared with placebo and ustekinumab treatment with respect to the ranked secondary endpoints of PASI 100, PASI 90, and PASI 75 scores; sPGA clear, sPGA clear or almost clear; DLQI score of 0 or 1; and PSS score at specified time points.

Statistically significant treatment effects favouring risankizumab were achieved for all ranked secondary endpoints in each study, indicating that risankizumab treatment was superior to placebo and ustekinumab (see Table 5).

Table 5: Studies M15-995 and M16-008 Analysis results of ranked secondary endpoints (Intention to Treat populations)

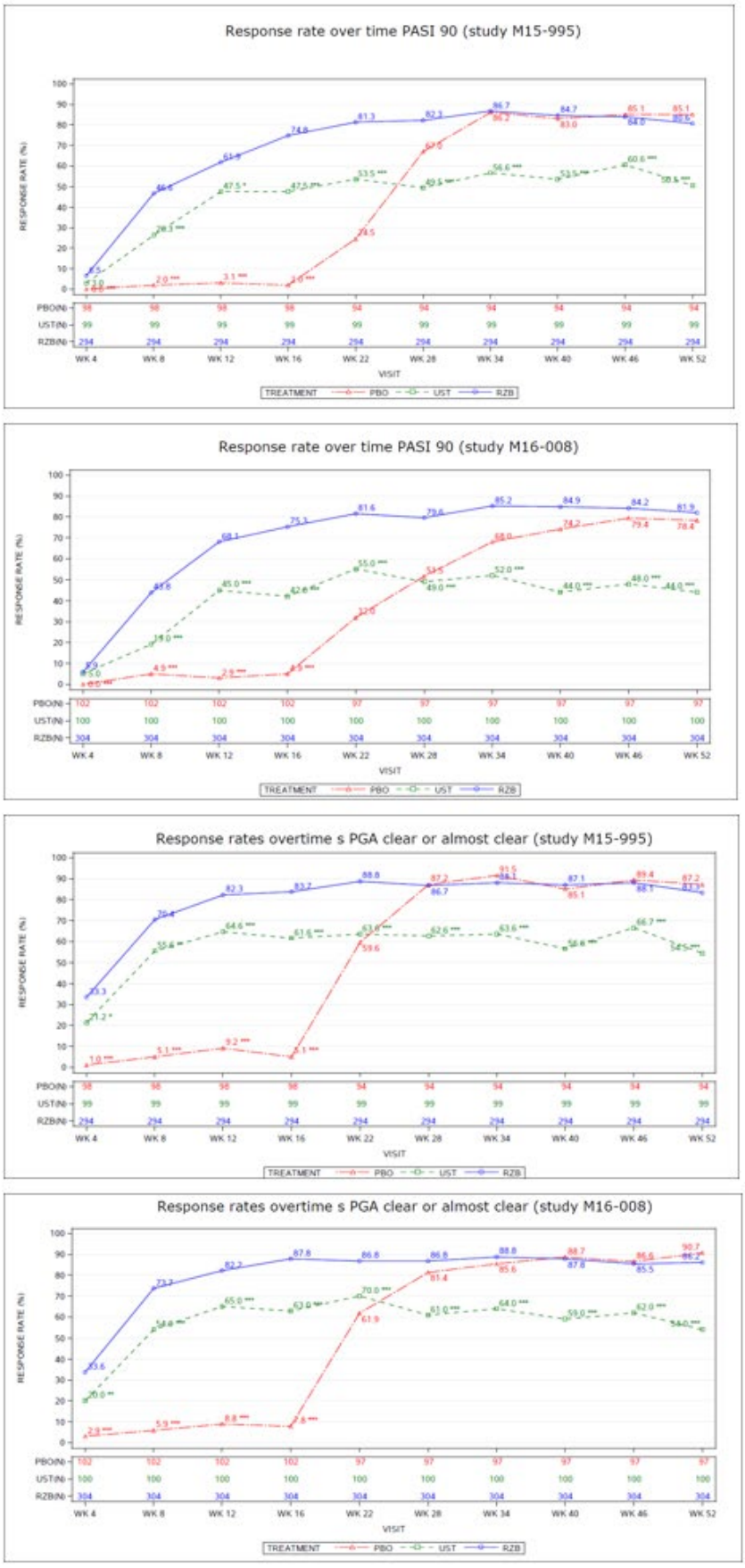
	M16-008			M15-995		
Response	Risankizumab (N = 304) n (%)	Ustekinumab (N = 100) n (%)	Placebo (N = 102) n (%)	Risankizumab (N = 294) n (%)	Ustekinumab (N = 99) n (%)	Placebo (N = 98) n (%)
sPGA of clear or almost clear (0 or 1)						
Week 12	250 (82.2)	65 (65.0)	9 (8.8)	242 (82.3)	64 (64.6)	9 (9.2)
Week 52	262 (86.2)	54 (54.0)	--	245 (83.3)	54 (54.5)	--
sPGA of clear (0)						
Week 16	112 (36.8)	14 (14.0)	2 (2.0)	150 (51.0)	25 (25.3)	3 (3.1)
Week 52	175 (57.6)	21 (21.0)	--	175 (59.5)	30 (30.3)	--
PASI 75						
Week 12	264 (86.8)	70 (70.0)	10 (9.8)	261 (88.8)	69 (69.7)	8 (8.2)
Week 52	279 (91.8)	70 (70.0)	--	269 (91.5)	76 (76.8)	--
PASI 90						
Week 52	249 (81.9)	44 (44.0)	--	237 (80.6)	50 (50.5)	--
PASI 100						
Week 16	109 (35.9)	12 (12.0)	0.0	149 (50.7)	24 (24.2)	2 (2.0)
Week 52	171 (56.3)	21 (21.0)	--	175 (59.5)	30 (30.3)	--

Notes: Analyses used non-responder imputation.
All comparisons of risankizumab versus ustekinumab and placebo achieved $P < 0.001$.

Starting at Week 12, statistically significant differences in favour of risankizumab for the proportions of subjects who achieved PASI 75/90/100 responses, as well as sPGA of

clear/clear or almost clear were observed through Week 16 compared with subjects in the placebo and ustekinumab groups. Subjects who received continuous risankizumab experienced persistent or increased responses through study completion, with approximately 60% of subjects achieving complete clearance at Week 52. Subjects who were randomised to placebo and then switched to risankizumab at Week 16 achieved similar response rates of PASI 90/100, as well as sPGA of clear and sPGA of clear or almost clear by the end of the study. Among subjects who entered Part B as PASI 100/90 and sPGA clear/clear or almost clear responders, (Study M16-008: 81.7%/88.6% and 81.3%/92.1%, Study M15-995: 78.5%/88.6% and 78.7%/89.4%) maintained their response at Week 52, respectively (see Figure 2).

Figure 2: Studies M15-995 and M16-008 Response rate over time (PASI 90 and PGA clear or almost clear responses)



Quality of life results

Statistically significant differences in favour of risankizumab compared to placebo were observed for improvement in patient-reported PSS, DLQI (see Table 6), Health Assessment Questionnaire Disability Index (HAQ-DI), and Hospital Anxiety and Depression Scale (HADS) responses.

Table 6: Health-related quality of life in Studies M15-995 and M16-008

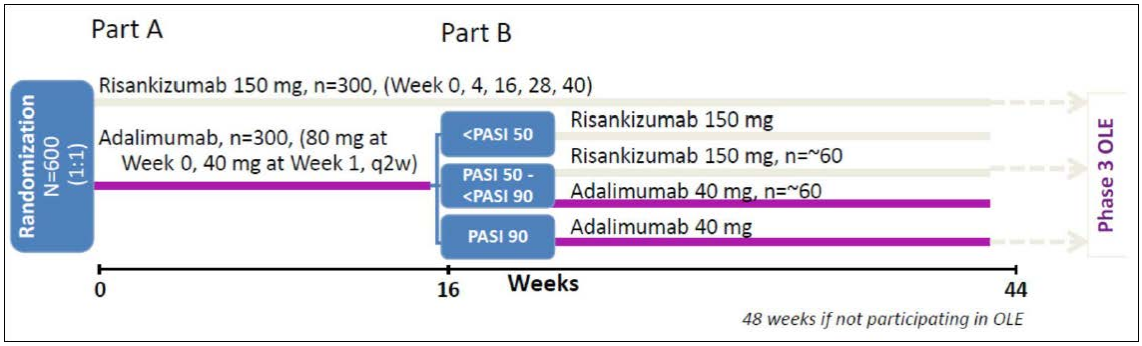
	Study M16-008			Study M15-995		
	RZB	UST	PBO	RZB	UST	PBO
DLQI 0 or 1	n/N (%)					
Week 16	200/304 (65.8)	43/100 (43.0)	8/102 (7.8)	196/294 (66.7)	46/99 (46.5)	4/98 (4.1)
Week 52	229/304 (75.3)	47/100 (47.0)	--	208/294 (70.7)	44/99 (44.4)	--

Analyses used non-responder imputation. All comparisons of risankizumab versus ustekinumab, adalimumab and placebo achieved $p < 0.001$.

Study M16-010

Study M16-010 was a multinational, randomised, double blind, double dummy, active controlled, parallel design study (see Figure 3) conducted at 66 sites in 11 countries (Canada, USA, Mexico, Poland, Germany, Portugal, France, Sweden, Finland, Czech Republic, Taiwan) from March 2016 to August 2017.

Figure 3: Study M16-010 design



Objectives

To assess the efficacy and safety of risankizumab compared with adalimumab in subjects with moderate to severe chronic plaque psoriasis after 16 weeks, and the efficacy and safety of switching to risankizumab compared with continued adalimumab in patients with an inadequate response to adalimumab at Week 16; and to assess the PK of risankizumab and emergence of anti-drug antibodies and their effect on efficacy and safety.

Patients eligible for enrolment were adults ages ≥ 18 years of age with stable moderate to severe chronic plaque psoriasis of ≥ 6 months duration; with or without PsA; BSA involvement ≥ 10%; PASI ≥ 12; sPGA ≥3; candidates for systemic or photo therapy; and candidates for adalimumab. Drug induced or non-plaque forms of psoriasis, active inflammatory diseases and PsA, known chronic or acute infections or who had previously received adalimumab or risankizumab were excluded.

Part A

The co-primary endpoints were:

- achievement of ≥ 90% reduction from Baseline in PASI 90 at Week 16; and
- achievement of an sPGA score of clear of almost clear at Week 16.

Ranked secondary endpoints were:

- achievement of ≥ 75% reduction from Baseline at Week 16; and
- achievement of 100% reduction from Baseline in PASI 100 at Week 16.

Part B

The primary endpoints were:

- achievement of an PASI 90 at Week 44 for those subjects who are re-randomised at Week 16.

Ranked secondary endpoint was:

- achievement of 100% reduction from Baseline PASI 100 at Week 44.

There were similar other endpoints to the previous studies so are not presented in detail, here.

Eligible subjects were randomised 1:1 in blocks stratified by weight (≤ 100 kg versus > 100 kg) and prior exposure to TNF antagonists (0 versus ≥ 1). As pointed out by the clinical evaluator, blinding was mentioned (double blinded, double dummy with matching placebos), but the method of blinding was not provided.

Results

Demographic characteristics were overall balanced between the adalimumab and risankizumab groups in Part A and in Part B. The treatment groups were balanced with regard to prior psoriasis medication history. Approximately 10% of subjects in each group had a diagnosis of PsA, and approximately 10% had suspected PsA.

The co-primary endpoints were achieved. A statistically significantly larger proportion of subjects in the risankizumab group achieved both PASI 90 and sPGA clear or almost clear at Week 16 compared with the adalimumab group (see Table 7). Sensitivity and per protocol analyses supported the primary analysis. Point estimates were consistently in favour of the risankizumab group across strata.

Table 7: Study M16-010 Proportion of subjects in adalimumab and risankizumab groups who achieved PASI 90 and sPGA clear or almost clear responses, non responder imputation (Intention to Treat population)

			Yes		No		Missing			Adjusted			Breslow-Day
Assessment	Treatment	N	n	%	n	%	n	%	Diff %	Diff %	95% CI[a]	*P* value[b]	*P*-value
PASI 90	ADA	304	144	(47.4)	147	(48.4)	13	(4.3)	25.1	24.9	(17.5, 32.4)	< 0.001	0.103
	RZB	301	218	(72.4)	76	(25.2)	7	(2.3)					
sPGA of clear or almost clear													
	ADA	304	183	(60.2)	107	(35.2)	14	(4.6)	23.5	23.3	(16.6, 30.1)	< 0.001	0.003
	RZB	301	252	(83.7)	42	(14.0)	7	(2.3)					

ADA = adalimumab; CI = confidence interval; Diff = difference; NRI = non responder imputation; PASI = Psoriasis Area and Severity Index; RZB = risankizumab; sPGA = Static Physician Global Assessment

a. Across the strata, 95% CI for adjusted difference was calculated according to the Cochran-Mantel-Haenszel test adjusted for the comparison of 2 treatment groups.

b. Across the strata, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

Treatment effects in all pre-specified subgroups were in favour of risankizumab with 95% CIs of the treatment difference excluding zero in the majority of the subgroups for PASI 90 and sPGA clear or almost clear (Table 8).

The primary endpoint in Part B was also achieved. Among subjects with an inadequate response to adalimumab (PASI 50 to < PASI 90 response at Week 16), a statistically significantly larger proportion of subjects who were re-randomised to risankizumab achieved a PASI 90 response at Week 44 compared with subjects who were re-randomised

to adalimumab (Table 9). Sensitivity and per protocol analyses supported the primary analysis.

Table 8: Study M16-010 Proportion of subjects re-randomised to adalimumab and risankizumab who achieved a PASI 90 response at Week 44, non-responder imputation, Intention to Treat population

		Yes		No		Missing			Adjusted			Breslow-Day
Treatment	N	n	%	n	%	n	%	Diff %	Diff %	95% CI[a]	*P*-value[b]	*P*-value
ADA/ADA	56	12	(21.4)	37	(66.1)	7	(12.5)	44.6	45.0	(28.9, 61.1)	< 0.001	0.126
ADA/RZB	53	35	(66.0)	16	(30.2)	2	(3.8)					

ADA = adalimumab; CI = confidence interval; Diff = difference; NRI = non responder imputation; RZB = risankizumab

a. Across the strata, 95% CI for adjusted difference was calculated according to the Cochran-Mantel-Haenszel test adjusted for the comparison of 2 treatment groups.

b. Across the strata, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

Table 9: Study M16-010 Proportion of re-randomised subjects who achieved a PASI 90 response at Week 44 by PASI score subgroup at entry to Part B, non-responder imputation, Intention to Treat population

	ADA/ADA	ADA/RZB	Adjusted	
Group	n/N (%)	n/N (%)	Difference %	*P* value[a]
All re-randomized subjects	12/56 (21.4)	35/53 (66.0)	45.0	< 0.001
Subjects with < PASI 75 at entry to Part B	4/16 (25.0)	9/18 (50.0)	29.8	0.021
Subjects with ≥ PASI 75 at entry to Part B	8/40 (20.0)	26/35 (74.3)	56.8	< 0.001

ADA = adalimumab; NRI = non responder imputation; RZB = risankizumab

a. Across the strata, *P*-value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

Study M15-992

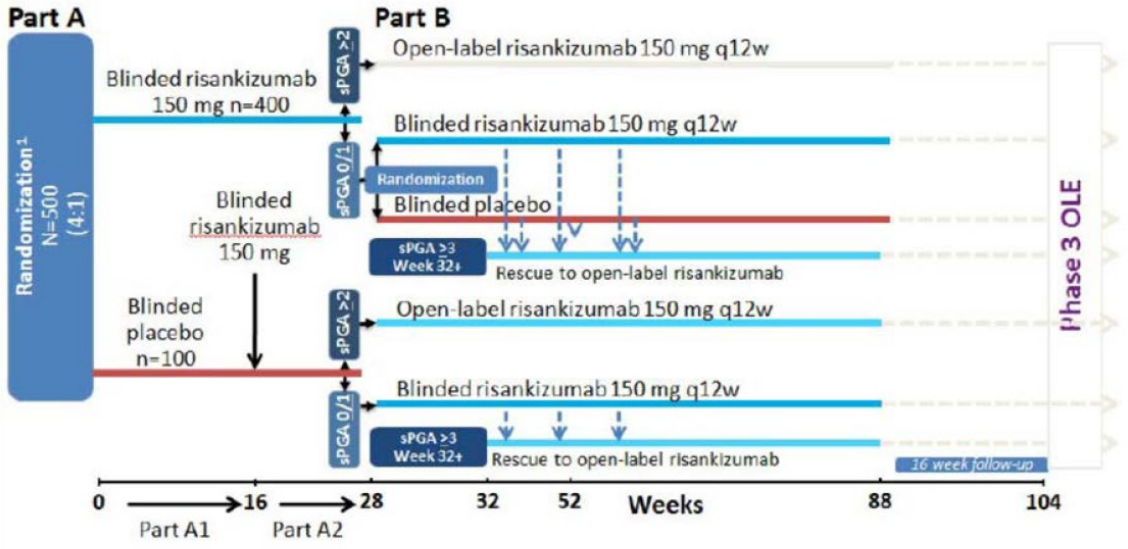
A multinational, multicentre, randomised, double blind, placebo controlled study conducted at 60 sites in nine countries (Australia, South Korea, Japan, USA, Canada, France, Belgium, Germany, and Czech Republic) from March 2016 to September 2017. Patient eligibility criteria were similar to previous studies.

Objectives

To assess the safety and efficacy of risankizumab 150 mg compared with placebo in subjects with moderate to severe chronic plaque psoriasis, the maintenance of response following drug withdrawal after Week 28 through Week 104, and the response after re treatment in subjects who experienced relapse after drug withdrawal and were re-treated with risankizumab; and to assess PK and the emergence of anti-drug antibodies, and the effect of anti-drug antibodies on efficacy and safety.

The study design comprised an 88 week treatment period and a 16 week follow-up period. All subjects had completed the double blind, placebo controlled part of the study (Part A1), and all continuing subjects had completed at least 52 weeks of study at the data cut-off date for this interim report.

Figure 4: Study M15-992 design



OLE = open-label extension; q12w = every 12 weeks; sPGA = Static Physician Global Assessment

The co-primary endpoints in Part A were:

- the proportion of patients achieving ≥ 90% reduction from PASI score at Baseline (PASI 90) at Week 16; and
- the proportion of patients achieving of an sPGA score of clear or almost clear (0 or 1) at Week 16.

The ranked secondary endpoints in Part A were:

- achievement of 75% reduction from Baseline PASI score (PASI 75) at Week 16;
- achievement of 100% reduction from Baseline PASI score (PASI 100) at Week 16;
- achievement of an sPGA score of clear (0) at Week 16; and
- achievement of a DLQI score of 0 or 1 at Week 16.

The ranked secondary endpoint in Part B was:

- achievement of sPGA of clear or almost clear (0 or 1) at Week 104.

Results

Demographic characteristics were overall balanced in both Part A and B. Overall, the majority of the subjects were male (70.2%) and White (79.3%) with 15.6% Asian and 3.9% Black/African American.

The co-primary endpoints were achieved. A statistically significantly larger proportion of subjects in the risankizumab group achieved both a PASI 90 and sPGA clear or almost clear response at Week 16 compared with the placebo group (Table 10). Sensitivity and per protocol analyses supported the primary analysis.

Table 10: Study M15-992 Co-primary endpoints in Part A, proportions of subjects with PASI 90 and sPGA clear or almost clear response at Week 16, non-responder imputation (Intention to Treat population)

			Yes		No		Missing			Adjusted			Breslow-Day
Assessment	Treatment	N	n	%	n	%	n	%	Diff %	Diff %	95% CI[a]	*P* value[b]	*P* value
PASI 90	PBO	100	2	(2.0)	93	(93.0)	5	(5.0)	71.2	70.8	(65.7, 76.0)	< 0.001	0.611
	RZB	407	298	(73.2)	102	(25.1)	7	(1.7)					
sPGA clear or almost clear													
	PBO	100	7	(7.0)	88	(88.0)	5	(5.0)	76.5	76.5	(70.4, 82.5)	< 0.001	0.447
	RZB	407	340	(83.5)	63	(15.5)	4	(1.0)					

CI = confidence interval; Diff = difference; ITT = Intent-to-Treat; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment

a. Across the strata, 95% CI for adjusted difference was calculated according to the Cochran-Mantel-Haenszel test adjusted for the comparison of 2 treatment groups.

b. Across the strata, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata. Within each stratum, *P* value was calculated based on the chi-square test (or Fisher's exact test if ≥ 25% of the cells had expected cell count < 5).

Treatment effects in all pre-specified subgroups were in favour of risankizumab with 95% CI of the treatment difference excluding zero in all subgroups for PASI 90 and sPGA clear or almost clear response.

The primary endpoint in Part B was achieved. A statistically significantly larger proportion of subjects who were re-randomised to continue risankizumab treatment in Part B achieved sPGA clear or almost clear response at Week 52 compared with subjects who were withdrawn from risankizumab therapy (re-randomised to placebo, Table 11).

Table 11: Study M15-992 Proportion of re-randomised subjects who achieved sPGA of clear or almost clear response at Week 52, non-responder imputation, Intention to Treat population

		Yes		No		Missing			Adjusted			Breslow-Day
Treatment	N	n	%	n	%	n	%	Diff %	Diff %	95% CI[a]	*P* value[b]	*P* value
RZB/RZB/PBO	225	138	(61.3)	49	(21.8)	38	(16.9)	26.1	25.9	(17.3, 34.6)	< 0.001	0.175
RZB/RZB/RZB	111	97	(87.4)	6	(5.4)	8	(7.2)					

CI = confidence interval; Diff = difference; ITT = Intent-to-Treat; NRI = non-responder imputation; PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment

a. Across the strata, 95% CI for adjusted difference was calculated according to the Cochran-Mantel-Haenszel test adjusted for the comparison of 2 treatment groups. Within each stratum, 95% CI for difference was calculated based on normal approximation to the binomial distribution.

b. Across the strata, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata. Within each stratum, *P* value was calculated based on the chi-square test (or Fisher's exact test if ≥ 25% of the cells had expected cell count < 5).

Among risankizumab subjects who achieved sPGA of clear or almost clear at Week 28, response was maintained better with continuous treatment versus withdrawal. This was supported by similar findings at other response levels. There were also higher response rates in PASI 90/100, as well as sPGA of clear, with continuous treatment compared with withdrawal. In all 4 response levels, continuous therapy was statistically significantly better than withdrawal from the treatment starting from Week 40.

Among sPGA responders at Week 28 who were re-randomised to placebo, relapsed, and received re-treatment, the vast majority regained sPGA of clear or almost clear. In fact, the response rate after re-treatment (85% sPGA clear or almost clear) was very similar to the response rate with initial treatment.

Among non-responders from Part A who were treated with risankizumab in Part B, approximately half achieved sPGA of clear or almost clear at Week 52.

Supportive study

Study 1311.2

There is only one supportive study (Study 1311.2). The study was primarily a dose finding study comparing three doses of risankizumab and dosing regimens (18 mg at Week 0 only; 90 mg at Weeks 0, 4, and 16; and 180 mg at Weeks 0, 4, and 16) compared with ustekinumab (45 mg or 90 mg weight based dosing at Weeks 0, 4, and 16). None of these doses are the dose and regimen proposed to be marketed.

The primary efficacy endpoint was achieved 73.2% of subjects in the risankizumab 90 mg group and 81.0% of subjects in the 180 mg achieved PASI 90 at Week 12 compared with 40.0% in the ustekinumab group. At the highest response levels (for example, PASI 90, PASI 100), the 180 mg risankizumab dose achieved the highest proportion of responders.

Pooled analysis

Consistent with the results seen in the individual studies, the co-primary endpoints for the placebo-controlled population, proportions of subjects who achieved PASI 90 and sPGA of clear or almost clear at Week 16, were achieved (Tables 12-13). Treatment effects in all subgroups were in favour of risankizumab with 95% confidence intervals of the treatment difference excluding zero in all subgroups (includes age, sex, race, body weight, baseline PASI score, concurrent PsA, previous receipt of a non-biologic systemic therapy, previous biologic treatment, and failure of previous biologic treatment) for PASI 90 and sPGA of clear or almost clear responses at Week 16.

Consistent with the individual study results, the co-primary and ranked secondary endpoints for the ustekinumab-controlled population, proportions of subjects who achieved PASI 90 and sPGA of clear or almost clear responses at Week 16, were achieved.

Table 12: Pooled Analysis, primary efficacy results (PASI 90 and sPGA clear or almost clear responses) at Week 16 in the Phase III risankizumab psoriasis studies, non-responder imputation (Intention to Treat Populations)

Study	PASI 90 n/N (%)			sPGA Clear or Almost Clear n/N (%)		
	Placebo	Risankizumab	*P*-value[a]	Placebo	Risankizumab	*P*-value[a]
M15-995 (1311.28)	2/98 (2.0)	220/294 (74.8)	< 0.001	5/98 (5.1)	246/294 (83.7)	< 0.001
M16-008 (1311.3)	5/102 (4.9)	229/304 (75.3)	< 0.001	8/102 (7.8)	267/304 (87.8)	< 0.001
M15-992 (1311.4)	2/100 (2.0)	298/407 (73.2)	< 0.001	7/100 (7.0)	340/407 (83.5)	< 0.001
	Adalimumab			**Adalimumab**		
M16-010 (1311.30)	144/304 (47.4)	218/301 (72.4)	< 0.001	183/304 (60.2)	252/301 (83.7)	< 0.001

a) Across the strata, p value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata. Within each stratum, p value was calculated based on the chi-square test (or Fisher's exact test if ≥ 25% of the cells had expected cell count < 5).

Table 13: Pooled Analysis, Primary efficacy results (PASI 90 and sPGA clear or almost clear responses) at Week 16, non-responder imputation (Placebo - Controlled Population)

Assessment	Treatment	N	n (%)	Adjusted Diff %	95% CI[a]	*P*-value[b]	Breslow-Day *P*-value
PASI 90	Placebo	300	9 (3.0)			< 0.001	0.683
	Risankizumab	1005	747 (74.3)	71.2	(67.9, 74.5)		
sPGA clear	Placebo	300	20 (6.7)			< 0.001	0.942
or almost	Risankizumab	1005	853 (84.9)	78.2	(74.7, 81.8)		

CI = confidence interval; Diff = difference; a) across the strata, 95% CI for adjusted difference was calculated according to the Cochran-Mantel-Haenszel test for the comparison of 2 treatment groups; b) across the strata, the p value was calculated according to the Cochran-Mantel-Haenszel test adjusted for strata.

Maintenance of response

A large proportion of subjects who received risankizumab and achieved a high level of response at Week 16 in Studies M15-995 and M16-008 maintained that response up to Week 52 (see Table 14).

Table 14: Studies M15-995 and M16-008 Maintenance of response in subjects who received risankizumab and achieved PASI 90, PASI 100, sPGA of clear, and sPGA of clear or almost clear at Week 16

	Assessment			
Time Point	PASI 90 n/N (%)	PASI 100 n/N (%)	sPGA Clear or Almost Clear n/N (%)	sPGA Clear n/N (%)
Week 22	431/450 (95.8)	224/258 (86.8)	490/515 (95.1)	228/262 (87.0)
Week 28	416/450 (92.4)	217/258 (84.1)	483/515 (93.8)	219/262 (83.6)
Week 34	429/450 (95.3)	210/258 (81.4)	486/515 (94.4)	214/262 (81.7)
Week 40	422/450 (93.8)	209/258 (81.0)	478/515 (92.8)	213/262 (81.3)
Week 46	410/450 (91.1)	212/258 (82.2)	472/515 (91.7)	217/262 (82.8)
Week 52	398/450 (88.4)	206/258 (79.8)	466/515 (90.5)	209/262 (79.8)

Notes: Subjects who received risankizumab in the Ustekinumab-Controlled Population are reported in this table.
Analysis used non-responder imputation.

Switching

Adalimumab to risankizumab

Among adalimumab responders (B_R (PASI 90) and Re-RAND to ADA (PASI 50 to < PASI 90)) at Week 16 Study M16-010) who completed the study on adalimumab and switched to risankizumab at entry of Study M15-997, the proportions of subjects who achieved PASI 75/90/100 (Table 15), sPGA of clear or almost clear, and sPGA of clear (Table 16) increased at Week 12 of Study M15-997.

Table 15: Study M15-997 PASI 75/90/100 responses in patients switched from adalimumab to risankizumab

	PASI 75		PASI 90		PASI 100	
	Re-Rand to ADA	B_R	Re-Rand to ADA	B_R	Re-Rand to ADA	B_R
Visit	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Entry of OLE	28/49 (57.1)	117/130 (90.0)	11/49 (22.4)	95/130 (73.1)	3/49 (6.1)	68/130 (52.3)
Week 12	25/27 (92.6)	63/64 (98.4)	21/27 (77.8)	59/64 (92.2)	9/27 (33.3)	50/64 (78.1)

ADA = adalimumab; OLE = open-label extension; RZB = risankizumab

Note: Re-rand to ADA: Subjects re-randomized to continue adalimumab at entry of Part B in Study M16-010 who switched from adalimumab to risankizumab in Study M15-997.
B_R: Adalimumab responders (subjects who achieved PASI 90) who continued with adalimumab at entry of Part B in Study M16-010 and switched from adalimumab to risankizumab in Study M15-997.
Analysis used last observation carried forward.

Table 16: Study M15-997 sPGA response of clear or almost clear, and sPGA response of clear in patients switched from adalimumab to risankizumab

	sPGA Clear or Almost Clear		sPGA Clear	
	Re-Rand to ADA	B_R	Re-Rand to ADA	B_R
Visit	n/N (%)			
Entry of OLE	16/49 (32.7)	102/130 (78.5)	3/49 (6.1)	68/130 (52.3)
Week 12	19/27 (70.4)	58/64 (90.6)	10/27 (37.0)	50/64 (78.1)

ADA = adalimumab; OLE = open-label extension; RZB = risankizumab

Notes: Re-rand to ADA: Subjects re-randomized to continue ADA at entry of Part B in Study M16-010 who switched from ADA to RZB in Study M15-997.

B_R: Adalimumab responders (subjects who achieved PASI 90) who continued with ADA at entry of Part B in Study M16-010 and switched from ADA to RZB in Study M15-997.

Analysis used last observation carried forward.

Ustekinumab to risankizumab

Table 17: Proportion of PASI and sPGA responders at Week 12 of Study M15-997 after switching to risankizumab at entry to study

		PASI 75	PASI 90	PASI 100	sPGA Clear or Almost Clear	sPGA Clear
Visit	N	Number of Subjects (%)				
Entry of OLE	169	132 (78.1)	80 (47.3)	46 (27.2)	99 (58.6)	46 (27.2)
Week 12	81	78 (96.3)	59 (72.8)	47 (58.0)	69 (85.2)	48 (59.3)

OLE = open-label extension; RZB = risankizumab; UST = ustekinumab

Note: Analysis used last observation carried forward.

Immunogenicity and efficacy

Overall, immunogenicity to risankizumab had no clinically relevant impact on the short-term efficacy (Week 16) or long-term (Week 52) maintenance of efficacy (as assessed by PASI 90 or sPGA 0/1 response).

Efficacy conclusion

The sponsor submitted a comprehensive clinical package consisting of five clinical studies (four pivotal and one supportive) which included both placebo and active comparators (adalimumab and ustekinumab). The response to the 150 mg given at Baseline (loading dose), 4 weeks and every 12 weeks was statistically significantly than placebo and compared to ustekinumab as well as adalimumab in patients moderate to severe plaque psoriasis. Maintenance of effect over 52 weeks was demonstrated in the 2 identical phase 3 studies and also over 44 weeks when compared to adalimumab. The results of the randomised withdrawal and re-treatment phase of study suggest that less frequent dosing interval or dosing based on patient's response.

The efficacy results demonstrated superiority of risankizumab over placebo at Week 16, and at Week 52, as the 95% confidence intervals of the treatment difference excluding zero in all subgroups. There was no clear subgroup identified interims of baseline disease, previous treatment of baseline demographics in which efficacy may not be optimal. The primary efficacy results were supported by the consistent results in the secondary outcomes.

Safety

The overall exposure to risankizumab exceeds the minimum numbers of patients recommended by the relevant ICH guideline;[13] however, as of the data cut-off date (1 September 2017) 4.3% were exposed for at least two years and only 1.3% were exposed for more than 3 years in clinical trials.[14] Nine integrated analysis populations characterised the safety profile of risankizumab. Three integrated analysis sets, the primary safety pool; ustekinumab controlled population; and the all risankizumab-psoriasis population, were identified by the sponsor as primary to characterising the safety and benefit/risk profile of risankizumab as they provide data regarding the short-term and long-term safety of risankizumab in subjects with psoriasis.

Of the total 2,234 subjects exposed to at least 1 dose of risankizumab (18, 90, 150, or 180 mg), 1,590 received at least 1 dose of risankizumab 150 mg with a total of 1,688.0 patient years (PY) of exposure. A total of 1,091 subjects received risankizumab 150 mg for ≥ 1 year. Only 3 patients received risankizumab 150 mg for greater than 18 months (see Table 18).

Table 18: Patient exposure to risankizumab

	Risankizumab 150 mg n (%)[a]	All Risankizumab n (%)[a]
All subjects (N) who received ≥ 1 dose	1590	2234
≥ 90 days (3 months)	1579 (99.3)	1971 (88.2)
≥ 180 days (6 months)	1561 (98.2)	1781 (79.7)
≥ 360 days (12 months)	1091 (68.6)	1208 (54.1)
≥ 540 days (18 months)	3 (0.2)	109 (4.9)
≥ 720 days (24 months)	0	96 (4.3)
≥ 900 days (30 months)	0	86 (3.8)
≥ 1080 days (36 months)	0	30 (1.3)
Total Patient-Years	1688.0	2166.6

a) As of 1 September 2017. Note: Exposure is calculated using 84 days past the final dose administration.

There were higher study discontinuation rates for the adalimumab (4.3%) and ustekinumab (9.6%) groups compared with the risankizumab 150 mg group (1.4%) and placebo group (3.7%). High study completions rates (95%) were maintained over 52 weeks for the ustekinumab controlled analysis group. Demographic characteristics, baseline morbidity and co-morbidity, as well as use of concomitant medications were generally well balanced across the treatment groups and between the safety analysis groups.

Treatment emergent adverse events

In the first 16 weeks of the Phase II and III psoriasis studies (Primary Safety Pool), the incidence rates of overall adverse events (AE) were higher than placebo but lower than those seen with ustekinumab and adalimumab. The rates of AE leading to discontinuation of study drug were low overall and occurred at a lower rate in the risankizumab 150 mg group (2.7 events/100 PY) compared to placebo (9.8 events/100 PY) ustekinumab (4.0 events/100 PY) and adalimumab (6.3 events/100 PY). At 16 weeks the exposure

[13] European Medicines Agency (EMA), Committee for Proprietary Medicinal Products (CPMP), ICH E1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95, June 1995.
[14] As of the March 2018 Safety Update Report, 6.6% were exposed for at least 2 years and 3.4% were exposed for at least 3 years (n = 2471, 3351.6 PY).

adjusted serious adverse event (SAE) and severe adverse event rate in the primary safety pool is lower for risankizumab 150 mg compared with the comparator groups (placebo, ustekinumab and adalimumab.

In the primary safety pool, representing the first 16 weeks of treatment in the Phase II and III studies, upper respiratory tract infections (URTI), viral URTI, headache, arthralgia, and fatigue were the most common AE occurring in at least 2% of subjects in the risankizumab group (150 mg or total populations). The reporting pattern of events at 16 weeks is similar across the risankizumab, placebo and ustekinumab treatment groups with a trend towards higher rates of AE in the adalimumab group. Injection site reactions like injection site erythema, pruritus, pain and swelling were lower for the risankizumab group.

At 52 weeks the most frequently reported AE (≥ 2% of subjects) reported with risankizumab treatment were viral URTI, URTI, arthralgia, headache, hypertension, fatigue, gastroenteritis, diarrhoea, back pain, influenza, sinusitis and folliculitis. Three new infections related adverse events were reported in this analysis, influenza (2.3%), folliculitis (2.0%) and sinusitis (2.3%). A number of AE reported in the 16 week analysis were not reported in this analysis (pruritus, cough, urinary tract infection (UTI), nausea, oropharyngeal pain).

Table 19: Most frequent adverse events reported in ≥ 1% of total risankizumab subjects, by frequency of Preferred Term in descending order (Primary safety pool, 16 Weeks)

				Risankizumab			
System Organ Class Preferred Term	Placebo (N = 300) n (%)	Ustekinumab (N = 239) n (%)	Adalimumab (N = 304) n (%)	90 mg (N = 41) n (%)	150 mg (N = 1306) n (%)	150 – 180 mg (N = 1348) n (%)	Total (N = 1389) n (%)
Any adverse event	145 (48.3)	125 (52.3)	173 (56.9)	23 (56.1)	638 (48.9)	658 (48.8)	681 (49.0)
Viral upper respiratory tract infection	13 (4.3)	13 (5.4)	24 (7.9)	7 (17.1)	77 (5.9)	83 (6.2)	90 (6.5)
Upper respiratory tract infection	9 (3.0)	10 (4.2)	12 (3.9)	1 (2.4)	55 (4.2)	55 (4.1)	56 (4.0)
Headache	6 (2.0)	8 (3.3)	20 (6.6)	1 (2.4)	44 (3.4)	47 (3.5)	48 (3.5)
Arthralgia	10 (3.3)	3 (1.3)	9 (3.0)	2 (4.9)	32 (2.5)	33 (2.4)	35 (2.5)
Fatigue	3 (1.0)	5 (2.1)	7 (2.3)	0	29 (2.2)	29 (2.2)	29 (2.1)
Back pain	1 (0.3)	3 (1.3)	6 (2.0)	1 (2.4)	21 (1.6)	22 (1.6)	23 (1.7)
Pruritus	4 (1.3)	4 (1.7)	10 (3.3)	1 (2.4)	19 (1.5)	21 (1.6)	22 (1.6)
Diarrhoea	5 (1.7)	7 (2.9)	6 (2.0)	0	17 (1.3)	18 (1.3)	18 (1.3)
Cough	0	1 (0.4)	2 (0.7)	1 (2.4)	16 (1.2)	17 (1.3)	18 (1.3)
Hypertension	6 (2.0)	3 (1.3)	8 (2.6)	0	15 (1.1)	15 (1.1)	15 (1.1)
Urinary tract infection	2 (0.7)	6 (2.5)	3 (1.0)	0	14 (1.1)	15 (1.1)	15 (1.1)
Nausea	1 (0.3)	3 (1.3)	3 (1.0)	1 (2.4)	14 (1.1)	14 (1.0)	15 (1.1)
Oropharyngeal pain	0	3 (1.3)	3 (1.0)	2 (4.9)	12 (0.9)	12 (0.9)	14 (1.0)
Gastroenteritis	3 (1.0)	2 (0.8)	1 (0.3)	2 (4.9)	12 (0.9)	12 (0.9)	14 (1.0)

Table 20: Most frequent adverse events reported in ≥ 2% of risankizumab subjects, by frequency of Preferred Term in descending order (Ustekinumab controlled analysis set, 52 Weeks)

System Organ Class Preferred Term	Ustekinumab (N = 199) n (%)	Risankizumab 150 mg (N = 598) n (%)
Any adverse event	157 (78.9)	419 (70.1)
Viral upper respiratory tract infection	42 (21.1)	90 (15.1)
Upper respiratory tract infection	26 (13.1)	70 (11.7)
Arthralgia	8 (4.0)	30 (5.0)
Headache	13 (6.5)	27 (4.5)
Hypertension	8 (4.0)	21 (3.5)
Fatigue	4 (2.0)	20 (3.3)
Gastroenteritis	6 (3.0)	19 (3.2)
Diarrhoea	10 (5.0)	18 (3.0)
Back pain	8 (4.0)	15 (2.5)
Influenza	5 (2.5)	14 (2.3)
Sinusitis	3 (1.5)	14 (2.3)
Folliculitis	6 (3.0)	12 (2.0)

In the overall risankizumab 150 mg safety analysis set at up to 77 weeks viral URTI and URTI, arthralgia and headache, hypertension, back pain and diarrhoea, influenza, UTI, gastroenteritis, sinusitis, fatigue, cough and bronchitis were the commonest adverse events. The majority of AEs including infections were of mild to moderate severity and were self-limiting and didn't result in discontinuation of study medication. Rates of severe AE were comparable across the three analysis sets. The System Organ Classes (SOCs) with the highest number of severe events were Cardiac Disorders SOC, Infections and Infestations SOC, Gastrointestinal Disorders SOC, Hepatobiliary Disorders SOC and Neoplasms SOC.

Serious adverse events

Thirty one (2.4%) subjects in the risankizumab 150 mg group had a SAE (9.9 events/100 PY), compared to 12 (4.0%) subjects in the placebo group (17.4 events/100 PY), 12 (5.0%) subjects in the ustekinumab group (18.4 events/100 PY), and 9 (3.0%) subjects in the adalimumab group (14.7 events/100 PY). There were no meaningful differences in the types of SAE across the treatment groups. The most frequently reported SAE in risankizumab treated subjects were infection-related events (mainly bacterial infections including pneumonia, sepsis, osteomyelitis and cellulitis), cardiac events and neoplasms.

Deaths

Overall, there were five deaths of subjects treated with risankizumab and 2 subjects treated with adalimumab reported in the psoriasis clinical studies. In the risankizumab treated patients the deaths were due to: acute myocardial infarction (MI), seizures (sudden cardiac death), metastatic liver cancer and two which were undetermined. One of the undetermined deaths occurred on Day 189, 161 days after last dose. The deaths in the adalimumab groups were due to gallbladder cancer and abdominal sepsis. There were no deaths reported in the clinical studies conducted in other (non-psoriasis) indications. As per analysis reported in European Medicines Agency (EMA) assessment, mortality rate in the risankizumab clinical studies was not higher than what would be expected in the general population after adjusting for country, age, and sex.

Adverse events of special interest

Adverse events of special interest evaluated were infections, malignancies, cardiovascular events, hepatic events, injection site and immune reactions, depression and suicidal behaviours.

Infections

The exposure adjusted infection rate for the overall risankizumab 150mg treated group (75.5 events/100 PY) was similar to the ustekinumab controlled group after 52 weeks of exposure. The proportion of infections classified as serious infections was low across all three analyses (< 2%). Although the overall serious infection for risankizumab is similar to other similar treatments the complication of serious infections with sepsis could suggest that the infections are more complicated. Serious infection will be monitored as part of a post marketing safety study. Clinically important active serious infection has been included as a contraindication and identified as important potential risk in the risk management plan (RMP).

Increases in fungal infections were reported in risankizumab treated patients compared to placebo and ustekinumab at 16 and 52 weeks. The potential risk for candida infections during treatment with novel biologic drugs such as risankizumab is a potential concern. Therefore, candida infections should be monitored using routine pharmacovigilance measures. Similarly herpes zoster infections will be monitored by the sponsor in the post approval setting.

Injections site reactions

The number of injection site reactions was low (69 subjects (3.1%)), with the most frequently reported injection site related AE (> 2 subjects) being injection site erythema in 33 (1.5%) subjects; injection site pain, injection site pruritus, and injection site reaction in 8 (0.4%) subjects each; injection site haematoma and injection site swelling in 7 (0.3%) subjects each; injection site haemorrhage in 6 (0.3%) subjects; and injection site bruising in 3 (0.1%) subjects. None of the injection site reactions were considered to be severe or led to discontinuation.

Hepatic

Overall, there was no signal of more potential for hepatotoxicity in risankizumab patients compared to placebo or comparator treatment over the short and longer term treatment term, but the Delegate agrees as suggested in the EMA report that incidence of 3 significant hepatobiliary SAE leading to discontinuation of study drug is a concern.

MACE events

The MACE rate in the risankizumab 150 mg group in the controlled portions of the studies (16 weeks of treatment) was 0.2 events/100 PY, compared to 1.1 events/100 PY in the placebo group. A total of two subjects in the Primary Safety Pool experienced a MACE: 1 cardiovascular death in the risankizumab 150 mg group and one nonfatal stroke in the placebo group. One additional subject in the risankizumab group experienced an extended MACE of hospitalisation for unstable angina. A total of 7 subjects in the primary safety pool experienced other cardiovascular events, 2 of which were on risankizumab (1 thrombotic event (pulmonary embolism) and 1 congestive heart failure). MACE is included as an identified potential risk in the RMP.

Malignancy

The exposure adjusted incidence rates of malignancies appear similar between risankizumab and ustekinumab (0.5 events/100 PY). But the overall exposure adjusted event rate in patients treated with risankizumab 150mg was higher at 1.5 events/100 PY. The overall event rate (1.5 events/100 PY) was slightly higher than the range (0.81 to 1.3 events per 100 PYs) reported for other non-TNF biologics in psoriasis population at

the time of their initial submission as presented by the sponsor. The malignancy event rate (1.4 events/100 PY) remained stable over the extended safety period covered in the analysis. There was no preclinical signal relating to malignancy for risankizumab. There is a well-established association between psoriasis and non-melanoma skin cancers, in particular squamous cell carcinoma associated with psoralen-PUVA-therapy. The safety data is limited considering the length of tumour induction, thus no conclusions concerning the possible cause of the slightly higher event rate of malignancies can be made. Malignancies are included as an important potential risk in the RMP. An additional pharmacovigilance study is proposed by the sponsor to the EMA to evaluate safety risks, including malignancies.

Hypersensitivity

Even though the association between hypersensitivity and treatment-emergent anti-drug antibodies was not established, warning regarding discontinuation of treatment if a serious hypersensitivity reaction occurs should be included in section 4.4 of the PI.

Depression/suicidal behaviours

The overall rates of depression and depression related events in risankizumab treated patients were low. No current evidence of causality of any of these events with risankizumab.

Laboratory

No clinical meaningful changes in haematology or clinical chemistry values. At 16 weeks the proportions of subjects with potentially clinically important changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin values in the risankizumab 150 mg group were recorded in < 2% of patients and were broadly comparable among treatment groups. Overall (up to Week 77) the proportions of subjects with potentially clinically important changes in ALT, AST, ALP, and bilirubin values in the risankizumab 150 mg group were recorded in < 3% of patients.

There is unclear finding with blood glucose risk in the submitted studies data. The sponsor is advised to evaluate the impact of risankizumab on blood glucose in all ongoing and planned studies.

Special populations

The overall rates of AE experienced in subjects ≥ 65 years of age and are comparable to the overall population however higher rates of SAE, AE leading to discontinuation, and severe AE were higher in the elderly population. Treatment-emergent AE reporting rates were slightly higher in females in both short and long term exposure. There were no clinically meaningful differences in safety between subjects who were anti-TNF naïve or experienced for AE, SAE, AE leading to discontinuation, and severe AE.

The current wording in section 4.6 of the PI is in line with the recommendations of the relevant guideline.[15] Pregnancy is included as missing information in the RMP and a dedicated cohort study of pregnancy exposures and outcomes in women with psoriasis, including mother-infant linkage, is planned. Breast feeding statement in the product information needs to align with the EU Summary of Product Characteristics (SmPC) which is less ambiguous.

Immunogenicity

The incidence of treatment emergent anti-drug antibodies (19%) at 16 weeks increased up to 24% after 52 weeks of risankizumab. A total of 9% and 14 % of patients treated at

[15] European Medicines Agency (EMA), Committee For Medicinal Products For Human Use (CHMP), Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling, EMEA/CHMP/203927/2005, July 2008.

the recommended dosing regimen developed neutralising antibodies (NAb) to risankizumab at 16 and 52 weeks respectively. The overall incidence of anti-drug antibodies and NAb appears to further increase following stopping then retreating with risankizumab. Despite the high levels of anti-drug antibodies, no subject exposed to risankizumab in the psoriasis studies experienced anaphylactic reactions or serum sickness-like reactions however, 2 subjects in the PsA studies did experience anaphylactic reactions.

The incidence of injection site reactions was higher among anti-drug antibody positive (2.7% and 5%) than the anti-drug antibody negative (1.3% and 3.3%) at 16 and 52 weeks, respectively. The sponsor provided additional data from Study M15-992 up to 104 weeks. The overall incidence of treatment emergent anti-drug antibodies and NAb are relatively high at 52 weeks (26% and 16%) following treatment with risankizumab but remain relatively stable (27% and 17%) over longer term follow-up up to 104 weeks. The incidences of injection site reactions are numerically higher in the anti-drug antibody positive than the anti-drug antibody negative groups at 16 and 52 weeks. The wording of section 4.8 of the PI should be revised accordingly. Addition of immunogenicity as an important potential risk in the RMP is not currently warranted.

Risk management plan

The sponsor has submitted core RMP version 1.0 (date January 2018; data lock point (DLP) 26 October 2017) and Australian Specific Annex (ASA) version 1.0 (date May 2018) in support of this application. The sponsor has committed to provide the EU RMP once it is approved by the EMA.

With the response to TGA questions the sponsor provided an updated core RMP version 1.1 (dated November 2018; DLP 26 October 2017) and an ASA version 1.1 (dated December 2018).

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 21. [16]

Table 21: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None				
Important potential risks	MACE	✓	✓	✓	–
	Serious infections	✓	✓	✓	–

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

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Malignancies	✓	✓	✓	–
	Serious hypersensitivity reactions	✓	✓	✓	–
Missing information	Use during pregnancy and lactation	✓	–	✓	–
	Use in patients with chronic hepatitis B (HBV) or chronic hepatitis C (HCV) infection	✓	–	✓	–
	Use in patients with any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix	✓	–	✓	–

- Routine pharmacovigilance measures include follow-up questionnaires to monitor all of the important potential risks and the missing information of 'Use during pregnancy'. Additional pharmacovigilance activities include a long term prospective study and a drug utilisation study during pregnancy. This pharmacovigilance plan is acceptable.
- Only routine risk minimisation measures are proposed. Routine risk minimisation measures are considered acceptable to mitigate the risks associated with this product.

Wording for conditions of registration

The suggested wording is:

> 'The Skyrizi Core-Risk Management Plan (RMP) (version 1.1, dated November2018; data lock point 26 October 2017), with Australian Specific Annex (version 1.1, dated December 2018), included with submission PM-2018-01889-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
>
> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As Skyrizi is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Skyrizi (risankizumab) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Skyrizi must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.'

Risk-benefit analysis

Delegate's considerations

Discussion

Overall, pharmacokinetics of risankizumab was well studied and characterised. Subjects with body weight > 100 kg were estimated to have approximately 30% lower risankizumab exposure than subjects with body weight ≤ 100 kg but it showed no impact on risankizumab efficacy as assessed by the PASI 90 and sPGA of clear or almost clear responses in the efficacy studies. The proposed dose and dosing regimen of 150 mg SC (given as two 75 mg injections) at Week 0, Week 4, and then subsequently Q12W is well supported by the dose finding studies and popPK/PD analyses submitted in the application. The TGA pharmacometrics working group supported the conclusions from the pharmacometrics evaluator, that the analysis is acceptable and supports the proposed dosing regimen. The working group did not identify any further issues in relation to popPK and PK/PD analyses.

The clinical efficacy was based on five clinical studies (four pivotal and one supportive) which included both placebo and active comparators (adalimumab and ustekinumab).

In the individual clinical studies and integrated analyses, subjects with moderate to severe plaque psoriasis who were treated with risankizumab 150 mg administered at Weeks 0 and 4 experienced substantial skin clearance and clinical improvement in the extent and severity of plaque psoriasis after 2 doses (Weeks 0 and 4), with Week 16 PASI 90 and sPGA clear or almost clear response rates that were consistent across the four pivotal studies. The PASI 90 responses ranged from 72.4% to 75.3% and sPGA clear or almost clear responses ranged from 83.5% to 87.8% in the five studies compared with placebo in three of the trials 2.0% to 4.9% for PASI 90 and for sPGA clear or almost clear 5.1% to 7.8%.

The results compared with the active comparators demonstrated superiority of risankizumab for the PASI 90 responses; adalimumab 47.4% versus risankizumab 72.4% and ustekinumab 44.7% versus risankizumab 75.1%, and for sPGA responses of clear or almost clear at Week 16; adalimumab 60.2% versus risankizumab 83.7% and ustekinumab 62.3% versus risankizumab 85.8%. It is notable that the results seen at Week 16 were achieved with only 2 doses; at Week 0 and Week 4. The dose schedule is then proposed to be every 12 weeks. The long-term studies (to 52 weeks) indicated that the efficacy was maintained with maintenance doses. The primary efficacy results were supported by the consistent results in the secondary outcomes.

Switching to risankizumab for subjects who had inadequate initial response to adalimumab (PASI 50 response to < PASI 90 at Week 16) also produced statistically significant improvement for PASI 90 at Week 44 (adjusted difference 45% $p < 0.001$). Across the pivotal studies significant improvements in patient-reported outcomes of DLQI (DLQI score of 0/1) and PSS (clinically meaningful change in both symptom and sign scores) were observed.

Overall incidence of anti-drug antibodies was 19% across the clinical programme with 8% incidence of NAb at 16 weeks. This was increased at Week 52 to anti-drug antibody 24% and NAb incidence 14%. Presence of anti-drug antibodies or NAb to risankizumab also did not impact treatment effect at either Week 16 or Week 52 but in the small number of patients it was observed that with high anti-drug antibody titres ≥ 128 did not achieve the same favourable results as the patients with anti-drug antibody titres < 128.

Even though the safety data has been submitted satisfies the ICH E1 safety guidance of > 1500 patients exposed;[13] (according to the safety update report (data cut-off 29 March 2018) 2471 patients have been exposed), only 6.6% of patients have been exposed to 2 years or more. This extent of exposure is insufficient to fully characterise the unfavourable effects particularly those with a long induction period (malignancy) or those that might change with repeat exposure over time (anti-drug antibody profile and immunological AE). The Delegate notes that there is ongoing long-term safety trial which should address these concerns.

Among the most common TEAE, infections is the most frequent at Week 16 and event rate was overall stable over long-term exposure. Even though the overall rate of serious infection is low and remained stable across short and long-term exposure, there were 5 reports of cellulitis and 7 reports of sepsis, 2 reports of osteomyelitis, 14 reports of herpes zoster (2 serious reports) and 5 reports of pneumonia in the overall risankizumab treated population, half of which were considered related to study drug by the investigator and two of which resulted in discontinuation of study drug. This risk needs to be further characterised in the post approval setting. There was an increased reporting rate for fungal infections in risankizumab treated patients compared to placebo and ustekinumab (over 16 and 52 weeks) possibly due to nature of risankizumab action (disruption of the IL-23 immune pathway).

Although there was no overall signal of more potential for hepatotoxicity in risankizumab patients compared to placebo or comparator treatment over the short and longer term treatment, the incidence of 3 significant hepatobiliary SAE leading to discontinuation of study drug is a concern.

The incidence of injection site reactions was numerically higher among anti-drug antibody positive than the anti-drug antibody negative subjects. Immunogenicity has a small but clinically relevant impact on injection site reactions. This should be included in section 4.8 of the PI.

Although the overall MACE event rate is low (0.5 events/100 PY), after adjusting for exposure, there was a slight trend towards increased numbers of MACE, and other cardiovascular events with exposure to risankizumab over the longer term. Overall the event rate of any malignant tumour (including non melanoma skin cancer) with risankizumab (all doses) was 1.3 events/100 PY and slightly higher at 1.5 events/100 PY for subjects treated with risankizumab 150 mg only. This is slightly higher than the rates of malignant tumours reported in the other similar biologics clinical programs (0.81 to 1.3 events/100 PY). An additional pharmacovigilance study is proposed by the sponsor to EMA to evaluate safety risks, including malignancies. The overall suicidal ideation and behaviour rate was low. Safety data in patients > 65 is limited which needs to be incorporated in the PI.

The Delegate agrees with the clinical evaluator that current wording in the indication does not accurately reflect the patient population studied ('Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator') and data presented. It is also noted that the additional wording is included on all the other systemic products which may be considered competitors to risankizumab and the wording should be consistent so as not to suggest a competitive advantage which has not been proven.

Overall efficacy of risankizumab has been robustly demonstrated in the treatment of moderate to severe plaque psoriasis. Onset was achieved near maximal effect at Week 16 and maintained until 52 weeks. The effect size was highly statistically significant, clinically relevant and superior to two active comparators. Risankizumab has a low rate of adverse events which is comparable to placebo and generally more favourable than ustekinumab and adalimumab. Concerns identified include fungal infections, blood glucose, malignancy, MACE over longer term exposure. Overall, based on the data presented, the beneficial effects outweigh the unfavourable effects seen in the clinical trials.

Deficiencies of the data

Deficiencies of the data include:

- long term safety data (will be reported by ongoing safety Study M15-997);
- risk of malignancy;
- impact on blood glucose;
- combination with topical or systemic steroids; and
- combining biologics.

Outstanding issues

The outstanding issues are:

- indication wording;
- long term safety; and
- the sponsor should explain the discrepancy in the key secondary endpoints mentioned in the study synopsis and study protocol (Studies M15-995/M16-008); one shows ranked with Week 16 other shows with Week 12.[11]

Conclusion

Overall, risankizumab is approvable as the quality, nonclinical and clinical evaluators (subject to PI changes) have all recommended approval. The Delegate considers that sufficient data and justification have been provided to support the registration of risankizumab on quality, safety and efficacy grounds for the treatment of moderate to severe plaque psoriasis in adults who are candidates for phototherapy or systemic therapy.

Proposed action

The Delegate has no reason to say, at this time, that the application for risankizumab should not be approved for registration.

Any approval is subject to taking into account all issues arising from the Advisory Committee on Medicines (ACM) deliberations and finalising matters pertaining to the PI, to the satisfaction of the TGA.

Request for ACM advice

1. What are ACM's views on the patient population studied, dose and indication sought by the sponsor for risankizumab?
2. Does the ACM consider that the safety of risankizumab in the proposed indication is sufficiently well characterised and communicated in the PI?
3. 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.

Advisory Committee considerations[17]

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

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Skyrizi, a 75 mg/0.83 mL solution of risankizumab for injection, supplied in prefilled syringe for subcutaneous injection.

The proposed indication considered by the ACM was:

> *Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults.*

The ACM agreed that Skyrizi had an overall positive benefit-risk profile for the revised indication:

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

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice.

1. What are ACM's views on the patient population studied, dose and indication sought by the sponsor for risankizumab?

The ACM advised that the dose and administration schedule were adequately supported by the data submitted.

The ACM was of the view that the proposed indication encompassed a wider population than that studied in the trials submitted. The ACM agreed that the sponsor's argument in relation to having a wider indication to allow for patients who may be contraindicated for phototherapy or systemic therapies was invalid. If a patient is a candidate for phototherapy or systemic therapy then the patient would still be eligible for the proposed agent, regardless if the patient had any contraindication to those therapies.

The ACM therefore advised that the indication should be revised to be consistent with the indications for similar approved agents and to be limited to patients who are candidates for phototherapy or systemic therapy.

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

2. Does the ACM consider that the safety of risankizumab in the proposed indication is sufficiently well characterised and communicated in the PI?

The ACM was of the view that the safety profile has been well characterised and a comprehensive risk mitigation plan has been proposed. The potential risks associated with treatment have been identified and further comprehensive studies with meaningful endpoints are both underway and planned.

3. 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.

The ACM noted that the demonstrated efficacy of risankizumab in the treatment of moderate to severe plaque psoriasis and the robust safety profile of risankizumab are commensurate with the profiles of other approved agents.

The ACM advised that the risk/benefit profile of risankizumab in the treatment of plaque psoriasis is favourable only for the population studied (that is, patients who are candidates for phototherapy or systemic therapies), which must therefore be reflected in the indication wording.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Skyrizi (risankizumab) 75 mg/0.83 mL solution for injection, indicated for:

> *Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults (18 years or older) who are candidates for phototherapy or systemic therapy.*

Specific conditions of registration applying to these goods

- Skyrizi (risankizumab) is to be included in the Black Triangle Scheme. The PI and CMI for Skyrizi must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Skyrizi Core-Risk Management Plan (RMP) (version 1.1, dated November 2018; data lock point 26 October 2017), with Australian Specific Annex (version 1.1, dated December 2018), included with submission PM-2018-01889-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

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

Therapeutic Goods Administration

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