28 February 2019
EMA/191996/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Skyrizi

International non-proprietary name: risankizumab

Procedure No. EMEA/H/C/004759/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Skyrizi
Applicant:	AbbVie Deutschland GmbH & Co. KG Knollstrasse 50 67061 Ludwigshafen am Rhein GERMANY
Active substance:	RISANKIZUMAB
International Non-proprietary Name/Common Name:	risankizumab
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, interleukin inhibitors (L04AC)
Therapeutic indication(s):	Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.
Pharmaceutical form(s):	Solution for injection
Strength(s):	75 mg
Route(s) of administration:	Subcutaneous use
Packaging:	Pre-filled syringe (glass)
Package size(s):	2 pre-filled syringes + alcohol pads

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List of abbreviations

%CV	% Coefficient of variation
ADA	Anti-Drug Antibody
ADA_RZB	All subjects who were switched from adalimumab to risankizumab 150 mg in Study M16 010) (1311.30) or Study M15-997
ALL_RZB	All Risankizumab-Treated (Population)
ANCOVA	Analysis of covariance
B_NR	Adalimumab nonresponders (subjects who did not achieve ≥ 50% reduction in Psoriasis Area and Severity Index score) who switched from adalimumab to risankizumab at entry of Part B in Study M16-010 and received risankizumab in Study M15-997
B_R	Adalimumab responders (subjects who achieved ≥ 90% reduction in Psoriasis Area and Severity Index score) who continued with adalimumab at entry of Part B in Study M16-010 and switched from adalimumab to risankizumab in Study M15-997
BI	Boehringer Ingelheim
BMI	Body mass index
BSA	Body surface area
BW	Body weight
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Peak plasma concentration
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CSS	Summary of Clinical Safety
CV	Cardiovascular
CYP450	Cytochrome P450
DAS28	Disease Activity Score 28
Diff	Difference
DLQI	Dermatology Life Quality Index
ECL	Electrochemiluminescent
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration

HADS	Hospital Anxiety and Depression Scale
HAQ-DI	Health Assessment Questionnaire Disability Index
HPC	High positive control
HPLC	High performance liquid chromatography
IgG	Immunoglobulin G
IL	Interleukin
IL23	Interleukin 23
ITT	Intent-to-treat
IV	Intravenous
LC-MS/MS	Liquid chromatography mass spectrometry
LOCF	Last observation carried forward
max	maximum
MI	Myocardial Infarction
ml	millilitre
NAb	Neutralizing antibody
NAPSI	Nail Psoriasis Severity Index
NL	No Load
NRI	Non-responder imputation
OL	Open-label
OLE	Open-label extension
PASI	Psoriasis Area and Severity Index
PASI X	Achievement of X% reduction from baseline PASI score
PBO	Placebo
PD	Pharmacodynamic
PFS	Pre-filled syringe
PK	Pharmacokinetic
PPASI	Palmoplantar Psoriasis Area and Severity Index
PRO	Patient-reported outcome
PsA	Psoriatic arthritis
PSS	Psoriasis Symptoms Scale
PSSI	Psoriasis Scalp Severity Index
PGA	Patient Global Assessment
PWG	Pathology Working Group

q12w	Every 12 weeks
RZB	Risankizumab
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SJC	Swollen joint count
SmPC	Summary of Product Characteristics
SOC	System Organ Class
sPGA	Static Physician Global Assessment
STAT3	Signal transducer and activator of transcription 3
TB	Tuberculosis
TJC	Tender joint count
TNF	Tumor necrosis factor
US	United States
UST	Ustekinumab
UST_RZB	Ustekinumab-to-Risankizumab (Population)vs. versus
Wk	Week

List of abbreviations – Quality

ADCC	Antibody dependent cellular cytotoxicity
AEX	Anion exchange chromatography
APG	Acidic Peak group
BPG	Basic Peak group
CDC	Complement dependent cytotoxicity
CDR	Complementary dependent region
CEX	Cation exchange chromatography
CFU	Colony forming unit
CGE	Capillary gel electrophoresis
CHO	Chinese hamster ovary
CO2	Carbon dioxide
CPP	Critical process parameter
CQA	Critical quality attribute
CV	Coefficient of variation

DHFR	Dihydrofolate reductase
DNA	Deoxyribonucleic acid
DoE	Design of experiments
ELISA	Enzyme-linked immunosorbent assay
FcRn	neonatal Fc Receptor
FMEA	Failure mode effect analysis
GMP	Good manufacturing practice
HC	Heavy chain
HCP	Host cell protein
HILIC	Hydrophilic interaction liquid chromatography
HMW	High molecular weight
ICH	International conference on harmonisation
IPC	In Process Control
JPE	Japanese Pharmacopoeia-Japanese Pharmaceutical Excipients
LC	Light chain
LC-MS	Liquid chromatography – mass spectroscopy
LMW	Low molecular weight
LOQ	Limit of quantitation
mAb	Monoclonal antibody
MCB	Master cell bank
MS	Mass spectroscopy
MTX	Methotrexate
MuLV	Murine Leukaemia virus
Mw	Molecular weight
NGNA	N-glycopneuraminic acid
NOR	Normal operating range
NSP	Needle stick protection
PC	Process characterisation
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDE	Permitted daily exposure
PFS	Pre-filled syringe
Ph. Eur.	European pharmacopoeia

PK	Pharmacokinetics
PPCB	Post production cell bank
PPQ	Process performance qualification
PS20	Polysorbate 20
QT	Qualification threshold
QTPP	Quality target product profile
RH	Relative humidity
SEC	Size exclusion chromatography
SPR	Surface plasmon resonance
SST	System suitability tests
STAT	Signal transducer and activator of transcription
TEM	Transmission electron microscopy
TSE	Transmissible spongiform encephalopathies
UF/DF	Ultrafiltration/ diafiltration
UP-SEC	Ultra-Pressure Size Exclusion Chromatography
USP	United States Pharmacopoeia
UV	Ultraviolet
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AbbVie Deutschland GmbH & Co. KG submitted on 26 April 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Skyrizi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Treatment of moderate to severe plaque psoriasis in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0205/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0205/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance risankizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Kiely Co-Rapporteur: Agnes Gyurasics

The application was received by the EMA on	26 April 2018
The procedure started on	24 May 2018

The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	17 August 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 August 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	30 November 2018
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: A GCP inspection was carried at 4 sites between August and November 2019: • Two clinical investigation sites in KR - Seoul National University Hospital and in Canada at Enverus Medical Research. • Two sponsor sites in US Abbvie and US Boehringer-Ingelheim Pharmaceuticals, Inc. The outcome of the inspection carried out was issued on 14 January 2019	14 January 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	07 January 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 January 2019
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	24 January 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	31 January 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	05 February 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 February 2019
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	22 February 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Skyrizi on	28 February 2019

2. Scientific discussion

2.1. Problem statement

The risankizumab psoriasis clinical development program designed to support the proposed indication included 4 pivotal Phase 3 studies of the dose and dosing regimen (risankizumab 150 mg subcutaneous [SC] injection at Weeks 0, 4, and every 12 weeks [q12w] thereafter) in adults who had stable moderate to severe chronic plaque psoriasis ≥ 6 months (with or without psoriatic arthritis), defined as body surface area (BSA) involvement ≥ 10%; Psoriasis Area and Severity Index (PASI) score ≥ 12; Static Physician Global Assessment (sPGA) ≥ 3.

The proposed indication is for treatment of moderate to severe plaque psoriasis when systemic treatment is needed.

The route of administration is subcutaneous. Risankizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis. After training in subcutaneous injection technique, patients may self-inject if deemed appropriate.

2.1.1. Disease or condition

Psoriasis is a chronic debilitating immunologic disease characterized 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%.

Psoriasis may be classified according to morphologic and clinical presentation: plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, generalized pustular and localized pustular psoriasis, and inverse or intertriginous psoriasis.

Plaque psoriasis is the most common form, affecting approximately 80% to 90% of patients. 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 estimated prevalence of 50% in patients with plaque psoriasis, presents a spectrum of challenges to patients: 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 stigmatization.

Psoriatic arthritis occurs in 30% or more of patients with psoriasis and involves joint pain and destruction, and patients with psoriatic arthritis have reduced quality of life (QoL) and functional capacity compared with psoriasis patients or healthy controls.

The uncontrolled inflammation of psoriasis may contribute to commonly associated comorbidities, including cardiovascular (CV) disease (including hypertension and increased risk for myocardial infarction, stroke, and CV death), obesity, type 2 diabetes, arthritis, and chronic renal disease. Psoriasis is also associated with serious psychiatric comorbidities, including depression, anxiety, and suicidality, as well as substance abuse.

Topical corticosteroids are commonly used for mild to moderate cases. Other topical medications include keratolytic agents, anthralin, coal tar, vitamin D analogs, and retinoids. For more widespread disease, phototherapy (ultraviolet B [UVB] or psoralen with ultraviolet A [PUVA]) is commonly used.

Systemic therapy, including methotrexate (MTX), cyclosporine, synthetic retinoids, and fumaric acid are often effective in patients with moderate or severe disease. Due to the 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 and are increasingly being used as first line systemic treatment options.

Anti-TNF agents such as etanercept, adalimumab, and infliximab are approved for the treatment of moderate to severe psoriasis. Ustekinumab, a p40 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 psoriasis, more recent data suggest that IL-23 is disproportionately involved in the maintenance of chronic psoriasis. Guselkumab, an IL-23 inhibitor, was approved in the US in July 2017 and in the EU in November 2017 for the treatment of adults with moderate to severe plaque psoriasis.

In addition, brodalumab, ixekizumab, and secukinumab, which target IL-17, are approved for the treatment of moderate to severe psoriasis.

Psoriasis manifests in a wide range of severities, affecting 2 to 3% of the general population with significant variation by geographic location and age. The prevalence of psoriasis varies in the EU from 0.6% to 8.5.

2.1.2. Aetiology pathogenesis and clinical presentation

Psoriasis is a chronic, immune-mediated inflammatory disease characterized by the hyper proliferation of keratinocytes and skin-infiltrating T-lymphocytes that overexpress pro-inflammatory mediators. The disease is a chronic, painful immune-mediated inflammatory skin disease and has a lifelong remitting and relapsing course with varying factors that trigger exacerbations in susceptible individuals, thus making treatment challenging. Psoriasis is also associated with serious comorbidities and significant psychosocial disability with negative impacts on quality of life. The uncontrolled inflammation of psoriasis may contribute to commonly associated comorbidities, including cardiovascular (CV) disease (including hypertension and increased risk for myocardial infarction, stroke, and CV death), obesity, type 2 diabetes, arthritis, and chronic renal disease. Psoriasis is also associated with serious psychiatric comorbidities, including depression, anxiety, and suicidality, as well as substance abuse.

The current therapeutic options for moderate to severe plaque psoriasis include phototherapy, topical agents (e.g., corticosteroids), conventional systemic therapy (e.g., cyclosporine, methotrexate, and oral retinoids), and biologic therapy including TNF-α antagonists (adalimumab, etanercept, infliximab), anti-IL12/IL23 and anti-IL17 (ustekinumab, secukinumab, ixekizumab).

The conventional therapies are associated with dose- and treatment-limiting options. The most common reasons for discontinuation of these therapies are lack of efficacy, adverse events (AEs), and treatment inconvenience.

The biologic agents have been associated with higher objective response rates in clinical trials. However, even with these newer agents, most patients do not achieve optimal efficacy, such as total skin clearance.

Although newer treatment options provide improved outcomes compared with traditional systemic therapies, there remains a significant unmet patient need for novel agents and mechanisms that can provide a rapid onset of effect, improved and sustained skin clearance, and minimization of drug-specific safety concerns (e.g. serious infections including opportunistic infections and tuberculosis, malignancies including lymphoma, immunogenicity and demyelinating neurologic events).

2.1.3. Management

The primary goal of psoriasis therapies is clearance of psoriatic plaques. Milder forms of psoriasis are typically managed with topical therapies, while more extensive or severe forms of psoriasis are typically managed with phototherapy or systemic therapy, which includes small molecules, usually given orally, and biologics, which are large molecules usually given by injection or infusion.

In clinical practice, tumor necrosis factor (TNF) antagonists were the first biological therapies approved for psoriasis and represent a current treatment option for moderate-to-severe chronic plaque psoriasis. Ustekinumab (human IgG1 /κ monoclonal antibody against the p40 subunit of both IL-12 and IL-23 cytokines), secukinumab (human IgG1 monoclonal antibody against IL-17A), and ixekizumab (human IgG4 monoclonal antibodies against IL-17A cytokine) have also been approved for the treatment of patients with moderate-to-severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy.

There are a small proportion of subjects who require biologic therapy due to a variety of reasons including lack of effectiveness, inadequate response or intolerant to conventional therapy. Many subjects do not achieve adequate response, as defined by subjects achieving at least a 75% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 75), with anti-TNF agents and find that current therapies can lose efficacy over time. Another concern is as this is a chronic condition compliance in psoriasis patients is found generally to be poor.

About the product

Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that is directed against IL-23 p19. The framework of the risankizumab antibody has been engineered with 2 mutations in the Fc region to reduce Fcγ receptor and complement binding. Binding of risankizumab to IL-23 p19 inhibits the action of IL-23 to induce and sustain T helper (Th) 17 type cells, innate lymphoid cells, γδT cells, and natural killer (NK) cells responsible for tissue inflammation, destruction and aberrant tissue repair.

Type of Application and aspects on development

This is an application for centralized procedure according to Art. 3(1) (mandatory scope) of Regulation (EC) 726/2004, Annex (1) (Biotech medicinal product).

The application has been submitted in accordance with Art. 8(3) (full application) of Directive 2001/83/EC.

The applicant applied for scientific advice in 2015.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection in pre-filled syringe containing 75 mg of risankizumab as active substance.

Other ingredients are: disodium succinate hexahydrate, succinic acid, sorbitol, polysorbate 20 and water for injection.

The product is available in pre-filled glass syringe with a fixed needle and needle cover, assembled in an automatic needle guard. Each pre-filled syringe contains 75 mg risankizumab in 0.83 ml. Skyrizi is available in packs containing 2 pre-filled syringes and 2 alcohol pads.

2.2.2. Active Substance

General information

Risankizumab is a humanized antibody which selectively binds to IL-23p19 and therefore inhibits binding of IL-23 to its receptor. Risankizumab is composed of two heterodimers of a heavy and a light polypeptide chain. Each heavy chain (HC) is composed of 449 amino acids and each light chain (LC) contains 214 amino acids. The antibody molecule contains a total of 12 intra-chain disulfide bonds, four within each of the two HCs and two within each of the two LCs. The framework of the antibody has been engineered with two mutations in the Fc region, Leu234Ala and Leu235Ala to reduce the potential effector function. The C-terminal lysine of the heavy chain has been deleted to reduce potential charge heterogeneity. Each HC contains a single N-linked glycosylation site at asparagine 297. The Mw is 146 kDa.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The active substance is manufactured at Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Ris, Germany. Appropriate evidence of GMP certification has been provided for each site involved in active substance manufacturing and testing.

The manufacture of risankizumab represents a standard manufacturing process for the manufacture of antibodies. It is achieved in three main parts, the upstream process, which produces the antibody, the downstream process, which purifies the antibody and the formulation of the active substance.

The manufacturing process is well described in the dossier and details of in-process controls and process parameter normal operating ranges (NORs) and proven acceptable ranges (PARs) are listed for each manufacturing step. The critical process parameters (CPPs) and in-process controls (IPCs) are also indicated.

Reprocessing is registered for certain unit operation steps. It was supported by data and appropriately justified.

Each manufacturing step is described in sufficient detail and the appropriate controls are listed. The registered in-process controls are considered appropriate for control of a mAb.

Control of materials

Details of compendial and non-compendial raw materials are provided. Acceptable specifications are registered for all non-compendial raw materials. No materials of human or animal origin are used in the manufacture of the active substance. The viral risk arising from the use of cell line media, reagents and materials has been appropriately discussed and addressed. The qualitative composition of the media and supplements used in the manufacturing process has been registered.

Details of developmental genetics and the establishment of the Master Cell bank (MCB) have been provided in line with ICH Q5B.

Characterisation of the cell banks has been carried out in line with ICH Q5D. The MCB, WCB and PPCB were tested for adventitious agents in line with ICH Q5A.

Control of critical steps and intermediates

Details of in-process controls (IPCs) and critical process parameters (CPPs) have been provided. IPCs are separated into those with action limits and those with specifications.For the upstream process, IPC action limits are registered. IPCs with specifications are registered only for the production bioreactor.For the downstream process, IPCs with action limits are registered for each manufacturing stepThere are no specification IPC limits for the downstream process, however taking into consideration the release specifications and the overall control strategy, this approach is accepted.

CPPs are defined in line with ICH Q8 as parameters that have impact on CQAs. The CPPs with their respective PARs and associated NORs are provided and considered acceptable. Overall the control strategy in terms of CPPs and IPCs is considered acceptable to ensure adequate control of the active substance manufacturing process. Hold times are supported by appropriate data.

Process validation

Process validation PPQ runs were carried out on consecutive commercial scale batches. IPC and process parameter results, including CPPs and non-CPPs, have been provided for each manufacturing step for the PPQ batches. All process parameters were within the registered NORs and all IPC results were within registered limits. No non-conformance events were reported. Therefore, the process validation data show that the process is capable of consistently manufacturing active substance batches within the established control ranges.

Impurity clearance data have been provided. Hold time data has been provided which supports the hold times registered. The currently available full scale resin and membrane lifetime data have been provided.

Manufacturing process development

A detailed description has been provided on the manufacturing process development, including the control strategy, manufacturing process history, process characterization studies, impurity clearance studies, and extractables and leachables assessment.

Process characterisation studies (PCS) used a risk assessment approach to identify the process parameters to further study in scale down models. The ranges of process parameters were challenged in the scale down models to establish the PARs. The scale down models were shown to be representative of commercial scale using an equivalency test statistical approach. The final registered ranges of the PARs have been appropriately supported by data.

Data has been provided in support of the resin reuse cycles.

Characterisation

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a humanized IgG1-type antibody. Studies were performed to characterize risankizumab with respect to primary structure, higher order structure, disulphide bonds, mass heterogeneity, charge heterogeneity, size heterogeneity, oligosaccharides, and biological function as well as structure/function relationships. Identity has been confirmed using adequate techniques.

The applicant did not measure ADCC or CDC activity but has presented a reasonable argument as to why risankizumab is very unlikely to exhibit effector function. Risankizumab demonstrates comparable binding compared to the wild-type IgG1 reference molecule.

In summary, the characterization is considered appropriate for this type of molecule.

Specification

The proposed panel of release tests cover identity, quantity, purity, potency, charge and microbial assurance. In general, the panel of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody both at release and shelf life. The specification acceptance criteria are clinically qualified.

Impurity clearance data has been provided by measuring the levels of each impurity at several steps in the downstream manufacturing process. The testing and qualification of impurity removal is considered comprehensive and sufficient information on the analytical method validation for impurity testing was provided. The product-related impurities are aggregates and fragments which are tested on active substance release.

Analytical methods

The analytical methods have been sufficiently well described and appropriately validated in accordance with ICH Q2(R1). The tests for clarity, colour, pH, osmolality, endotoxin and bioburden are performed according to the Ph. Eur.

Batch analysis

Batch analysis data is provided.The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

A standard approach for two tier reference standards is in place. Both the primary and working reference standards have been sufficiently characterised. The procedure for assigning potency to new reference standards has been described and is considered sufficient to prevent any potential future drift in potency between standards. A protocol for qualification of future reference standards is provided and is acceptable.

Stability

Stability data has been provided in support of the claimed shelf life. The stability studies were in general performed in accordance with ICH Q5C. Overall the data provided support of the claimed shelf-life for active substance.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is supplied as a sterile solution in a single-use, prefilled syringe (75 mg risankizumab / 0.83 ml) assembled into a needle stick protection (NSP) device. The finished product formulation consists of risankizumab as the active substance, sorbitol, disodium succinate hexahydrate, succinic acid, polysorbate 20 and water for injections. All excipients are compendial, complying with either Ph. Eur., USP/NF or JPE, and have been used in other centrally authorised parenteral medicinal products.

The primary packaging is pre-filled glass syringe with a fixed needle and needle cover, assembled in an automatic needle guard. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

All excipients are well known pharmaceutical ingredients and their quality is of compendial grade. There are no novel excipients used in the finished product formulation.

The quality target product profile and critical quality attributes (CQAs) of the finished product were outlined and are appropriate for a monoclonal antibody.

Pharmaceutical development

The robustness of the formulation has been adequately demonstrated.

In addition, traceability of formulated product has been assured.

The manufacturing process has changed during development. Comparability of process batches, characterisation testing and stability data are acceptable. Process characterisation was conducted. Product homogeneity is further assured by the results of PPQ data.

An assessment of leachables and extractables from product contact material of the manufacturing process was conducted and it was concluded that the material poses no risk with regard to leachables. Some elemental impurities were identified but they were below the PDE limits as defined in ICH Q3D and therefore acceptable.

A range of studies was conducted adequately demonstrating the functionality of the primary container closure system. No impurities of safety concern were identified from leachable, extractable or elemental analysis studies. The choice of primary container closure system is considered to be appropriately justified.

Manufacture of the product and process controls

The finished medicinal product manufacturer is Boehringer Ingelheim Pharma GmbH & Co. KG located in Germany. Appropriate evidence of GMP certification has been provided for each site involved in finished product manufacturing and testing.

The manufacturing process for the pre-filled syringe is standard and involves: thawing of the active substance, homogenisation of the active substance and excipients, sterile filtration, filling and plunger stopper setting and visual inspection. A detailed description of the needle stick protection pre-filled syringe (NSP-PFS) final assembly and packaging process was also provided.

Process parameters, proposed acceptable ranges and justifications are presented for both critical and non-critical parameters. The IPC tests and proposed limits are acceptable.

All CQAs are included in the release specifications for the finished product.

The manufacturing process was validated based on production of consecutive batches at routine production scale. The validation is acceptable and the process is demonstrated to be capable of producing batches of consistent quality. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are considered to be adequate.

Product specification

The tests included in the proposed release and shelf life specifications for the finished product generally comply with the Ph. Eur. monographs for Monoclonal antibodies for human use. Release and shelf life specifications for the NSP-PFS are also provided and consist of tests for appearance and functionality. These are acceptable.

In general, the panel of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody finished product both at release and shelf life. These include tests for appearance and description, general tests, identity, heterogeneity, purity, potency, quantity, functional

tests, microbiological tests and excipients. Limits for pH and endotoxin have been tightened appropriately. This has been registered in the dossier.

Analytical methods

The majority of the analytical methods are either pharmacopoeial methods or the same methods as those used to test the active substance. For finished product specific methods, adequate descriptions have been provided. Descriptions are also provided for testing of the NSP-PFS. These do not require validation.

Batch analysis

Batch analysis data was provided for finished product batches. The results for all batches complied with proposed release specifications. Batch to batch consistency was demonstrated for each parameter analysed.

Batch analysis data is also provided for NSP-PFS batches from finished products.

Reference materials

For finished product tests, the same reference materials are used as for active substance.

Stability of the product

The proposed shelf life for the finished product is 24 months at 5 ± 3 °C. The stability studies were performed in accordance with ICH Q5C. The shelf life is supported by primary stability data.

A photostability study was performed compliant with ICH Q1B. The results demonstrated that the product should be stored protected from light and an appropriate warning has been included in the product information.

Stability studies were performed with finished product lots assembled into the NSP-PFS. Batches met the NSP-PFS shelf life acceptance criteria at all storage conditions. The accelerated aged batches met the NSP-PFS acceptance criteria.

Data provided supports the proposed shelf life of 24 months for finished product when stored at 2 -8 ºC.

Adventitious agents

The production cell line was derived from the CHO cell line. All animal derived materials are in compliance with the CPMP/CVMP/TSE Note for Guidance EMA/410/01. EDQM certificates of suitability are provided where available. From the MCB onwards, no raw materials of human or animal origin are used in the active substance or finished product manufacturing process for risankizumab, while those used during development of the cell line MCB have been appropriately documented and the viral and TSE risks are considered negligible.

The MCB and WCB are extensively screened for viruses and routine in-process testing for viral and non-viral adventitious agents is also performed on unprocessed bulk materials.

Viral clearance studies in accordance with ICHQ5A were performed on commercial scale material. The full viral clearance validation reports have been provided, demonstrating that viral safety is assured.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. No Major Objections were raised as regards the quality documentation. A number of deficiencies (Other Concerns) were observed but have been satisfactorily addressed.

The applicant has applied QbD principles in the development of the active substance and the finished product and their manufacturing process. A design space is claimed for the potency assay and multivariate ranges for several factors are registered for the method. The available data supports the proposed design space for the assay.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends some points for investigation.

The applicant shall review the specifications for the active substance and the finished product when sufficient number of batches have been released and tighten specification limits for potency, purity and impurity parameters if appropriate and justified.

2.3. Non-clinical aspects

2.3.1. Introduction

Risankizumab (INN) is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor complex. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses.

The applicant submitted a comprehensive non clinical package in support of human administration.

2.3.2. Pharmacodynamics

Primary Pharmacodynamics

Risankizumab specifically binds to the p19 subunit of IL-23 with high affinity, it does not bind to the p40 subunit of IL-23 which is also a subunit of IL-12. The epitope was determined to be located within the p19 subunit, there was no binding observed to the p40 subunit. Also, there was no specific effect on the on-rate or overall affinity of risankizumab in the presence of human serum.

In *in vitro* pharmacology assays risankizumab binds to human IL-23 with a dissociation constant (Kd) of ≤ 29 pM. High affinity binding of risankizumab to cynomolgus monkey IL-23 was also demonstrated with a Kd of less than 1 pM. Risankizumab has a higher affinity for the p19 subunit of cynomolgus monkey IL-23 than the human p19 subunit of IL-23, however this may be due to the detection limit of the surface platon resonance (SPR) technology used.

Binding is specific with no detectable binding to human IL-12 at a concentration of 1 µM. No binding to rat IL-23 was observed at concentrations of up to 1 µM, the same top concentration tested for human IL-12 binding. Binding to mouse IL-23 was significantly decreased with a Kd of 15 nM.

Risankizumab inhibits cynomolgus monkey and human IL-23 functions, but not mouse or rat. Risankizumab potently inhibits human IL-23 induced phosphorylation of signal transducer and activator of transcription 3 (STAT3) in the human B lymphoblast cell line DB with an IC_{50} value of 24 pM.

Additionally, risankizumab inhibits the induction of IL-17 by human and cynomolgus monkey IL-23 in mouse splenocytes, but does not inhibit the induction of interferon gamma (IFNγ) by human IL-12 in phytohaemagglutinin (PHA) blasts. In an in vivo mouse ear thickening model, risankizumab inhibits human IL-23-induced ear thickening as well as the induction of tissue IL-17 and IL-22.

Secondary Pharmacodynamics

Specific studies evaluating secondary pharmacodynamics of risankizumab have not been conducted. As a highly specific antibody against IL-23 the lack of secondary pharmacodynamics studies is acceptable.

Safety Pharmacology

Safety pharmacology-related endpoints were incorporated into the two Good Laboratory Practice repeat-dose cynomolgus monkey toxicology studies. Cardiovascular parameters evaluated included heart rate, PR, QRS, RR, QT and QTc intervals. Other parameters evaluated included clinical observations, ophthalmology, and neurobehavioral evaluations. Risankizumab did not demonstrate any effect on neurological, respiratory, or cardiovascular function including electrocardiograms, in the four-week and 26-week toxicology studies.

Overall risankizumab is a highly potent and selective monoclonal antibody for the p19 subunit of IL-23, in both cynomolgus monkey and humans. The provided non-clinical pharmacology package can be considered sufficient to support the marketing authorisation application in psoriasis patients.

2.3.3. Pharmacokinetics

In the single- and 4 week repeat-dose studies in cynomolgus monkeys, a validated ELISA method was used for the measurements of risankizumab. In the remaining repeat-dose studies in cynomolgus monkeys the method was transferred to another analytical CRO and revalidated, the calibration range remained the same. Two validated ligand-binding ADA assays (first and second generation) were applied that used an electrochemiluminescence (ECL) detection principle.

The risankizumab pharmacokinetic and immunogenic profile was characterized after a single intravenous or subcutaneous dose in female cynomolgus monkeys. Repeat dose TK was evaluated as part of the toxicology studies in cynomolgus monkeys. The risankizumab pharmacokinetic profile after a single dose was typical of a monoclonal antibody, with low volumes of distribution (Vss 40.7 mL/kg), low clearance (CL 0.243 mL/hr/kg) and a long terminal elimination half-life of 173 hours (7.2 days) following a single 1 mg/kg intravenous dose in cynomolgus monkeys. The terminal half-life following a 1.5 mg/kg subcutaneous dose averaged 7.7 days, with 71.8% bioavailability.

Two repeat dose studies characterized the risankizumab pharmacokinetics following weekly 5, 20 or 50 mg/kg intravenous or subcutaneous administration. At treatment durations ranging from 4 to 26 weeks,

there were no consistent differences in exposure between male and female monkeys. Risankizumab exposures were roughly proportional to the administered doses, with accumulation in agreement with the observed half-life and dosing interval. In the 4-week study, systemic exposure of risankizumab following subcutaneous administration of 20 mg/kg was lower than that following intravenous administration at the same dose level, with a mean SC/IV AUC0-168hr ratio averaging approximately 45% in both Week 1 and Week 4. In the 26-week study where risankizumab was dosed at 5, 20 and 50 mg/kg SC, some degree of accumulation was observed. The Cmax and AUC0-168hr values of risankizumab in Weeks 4 and 26 were generally greater than those in Week 1; exposures in Week 26 were comparable to those in Week 4. No consistent difference in risankizumab exposure was observed between males and females in Weeks 1, 4 and 26.

Although the metabolic pathways of therapeutic mAbs are unknown, the expected consequence of metabolism of biotechnology derived mAbs is the catabolism to small peptides and individual amino acids in the same manner as endogenous IgG. Therefore, classical biotransformation studies as performed for small molecule pharmaceuticals are not needed for therapeutic mAbs (ICH S6 [R1]).

Following single administration of risankizumab to monkeys and humans, differences in certain PK parameters were observed. Following IV infusion of 1 mg/kg, Cmax of 61.4 µg/ml was measured in monkeys compared to 12.3 µg/ml in humans. Following SC administration of 1.5 mg/kg Cmax was 16.1 µg/ml in monkeys and 5.73 µg/ml in humans. There were also differences observed in the half-life of risankizumab in monkeys compared to humans, in monkeys the 173 hours following IV infusion and 184 h following SC administration. In humans the half-life was 665 hours following either IV or SC administration. As half-life is a combination of clearance and volume of distribution, the longer half-life in human is attributed to the higher volume of distribution. It is noted that the Tmax after IV administration of a dose of 1 mg/kg (10 minutes constant rate infusion) was 2 hours, which is unusual for IV administration, although in these animals, sampling was only performed at 10 minutes and 8 hours (and later time points) after administration, which may, together with the slow distribution and clearance, explain the relatively high mean Tmax in this study.

Risankizumab is a typical IgG monoclonal antibody targeting a soluble target, distribution is assumed to be limited to the vascular space with limited distribution to the extracellular space due to its size and hydrophilicity. The expected consequence of metabolism of biological products is degradation to small peptides and amino acids, and elimination via catabolism. On the basis of that any potential small molecule co-dosed with risankizumab is unlikely to share the same elimination mechanisms as this antibody. Nonetheless inhibition of IL-23 by risankizumab in patients may suppress directly or indirectly the pathophysiological expression of downstream cytokines such as IL-17, IL-6, IL-10, IFNγ and TNF-α. Some of these cytokines are known to impact CYP isoforms. A clinical study carried out by the applicant demonstrated that 150mg risankizumab administered SC every four weeks had no effect on the AUC of CYP probe drugs or their metabolites. Clinically relevant drug interactions are not expected.

In the 4-week repeat dose study, only monkeys in the highest IV dose group (8/10 at 50 mg/kg) were anti-drug antibody (ADA) positive at more than one consecutive time point based on a screening assay. The incidence of ADA was low in the 26-week general toxicity study, with two of 12 monkeys in the control group, one of eight monkeys in the 5 mg/kg group and six of 12 monkeys in the 50 mg/kg group exhibiting the presence of confirmed ADAs. The incidence of ADA was also low in the enhanced pre- and postnatal developmental (ePPND) toxicity study, with 9/21 monkeys in the 50 mg/kg treatment group confirmed positive. In general, samples with confirmed positive anti-risankizumab antibody had ADA signals just above the cut-point of the assay. Animals with confirmed ADA positive status were generally only either transiently or intermittently ADA positive during the course of the study. The presence of confirmed positive ADA status did not appear to affect the serum concentrations of risankizumab.

In a pre-postnatal study with 5 or 50 mg/kg/week subcutaneous doses of risankizumab in cynomolgus monkeys, samples for serum concentration analysis were obtained from the dosed mothers and corresponding infants 14, 28 and 91 days after birth. Measurable risankizumab concentrations were maintained for at least 91 days postpartum in most adult female monkeys and all infants. The mean infant serum exposures were 25% and 17% of the mean maternal serum exposures on Birth Day (BD) 14 in the 5 and 50 mg/kg/week treatment groups, identifying the ability of risankizumab to cross the placenta.

2.3.4. Toxicology

The nonclinical toxicity studies were intended to assess the systemic and local toxicity of risankizumab using relevant animal species is described in ICH S6(R1). The relevant animal species chosen was the cynomolgus monkey. The cynomolgus monkey was the only relevant species due to insufficient cross-reactivity of risankizumab to IL-23 from rodents. Risankizumab showed high binding affinity and potency against both human and monkey IL-23. In cynomolgus monkey at the NOAEL of 50 mg/kg exposure levels 69-fold greater than the highest exposure levels in human subjects were observed following SC administration, which is the intended clinical route of administration.

Repeat dose toxicity

Repeat dose toxicity of risankizumab was evaluated in a four-week study after IV administration of up to 50 mg/kg/week and at 20 mg/kg/week after SC administration, and in a 26 week chronic study with subcutaneous doses of up to 50 mg/kg/week. Reversibility of effects after an 8-week recovery period was tested in both studies in the control and high-dose groups.

In the four-week study, risankizumab was well tolerated at all dose levels, with no evidence of test item-related effects on clinical signs, body weight, ophthalmology, neurobehavioral evaluations, clinical pathology (pretest, termination, at end of recovery), electrocardiograms, organ weights, macroscopic observations and microscopic pathology. Nine of ten 50 mg/kg IV animals had positive results for ADAs, but the presence of ADAs did not appear to affect the systemic exposure to risankizumab and did not produce any ADA-dependent safety findings (e.g., hypersensitivities). The NOAELs were 50 mg/kg/week for IV administration and 20 mg/kg/week for SC administration; the corresponding exposure levels at week 4 (meanAUC0–168hr of 92 mg•hr/mL and 27 mg•hr/mL respectively) were 74-fold (IV) and 21-fold (SC) greater than the highest exposure level in human subjects.

In the 26-week study, risankizumab was administered SC to male and female cynomolgus monkeys (four/sex/group) at 0, 5, 20 and 50 mg/kg/week; two animals/sex/group from the control and high dose group went into an eight-week recovery period. No deaths occurred during the study, and no risankizumab-related effects were seen in clinical observations, body weight, food consumption, organ weights, body temperatures, blood pressure (indirect measurement), ophthalmology, electrocardiography, veterinary physical examination findings, neurobehavior assessments, clinical pathology parameters, lymphocyte phenotyping, T-cell dependent antibody response, and macroscopic or microscopic pathology findings. No evidence of opportunistic infections or precancerous microscopic changes was observed. Systemic exposure (Cmax and AUC0-168hr) to risankizumab generally increased proportionately with dose on Day 1, Weeks 4 and 26 and some degree of accumulation was observed. ADA positive results were observed in one of eight and six of twelve animals in the 5 and 50 mg/kg/week groups, respectively. Serum risankizumab concentrations were unaffected by ADAs and no ADA-dependent safety events were observed. The ADAs did not block the ability of risankizumab to bind to the IL-23 target in the IL-23 target capture assay. The NOAEL in this study was the highest dose tested (50 mg/kg/week) with an exposure level at Week 26 being 69-fold greater than the highest exposure in human subjects (a mean corresponding AUC0–168hr of 86 mg•hr/mL)

In a 26-week repeat-dose reproductive toxicity study in sexually mature male monkeys at 50 mg/kg/week, no risankizumab-related effects on reproductive parameters (that included a stage-dependent histopathological evaluation of spermatogenesis) were found. An initial concern regarding potential disruption of spermatogenesis in monkeys was determined after review by specialists in veterinary pathology to be unrelated to risankizumab, but due to the inclusion in the 26-week study of several monkeys that did not fully reach sexual maturity being included. The overall conclusion is that male and female fertility was not affected by chronic exposure to risankizumab at doses up to 50 mg/kg/week, and this is reflected in section 4.6 of the SmPC.

The risankizumab toxicological assessment conducted in cynomolgus monkey did not identify any toxicologically significant findings in any of the repeat-dose studies. The NOAEL was 50 mg/kg/week, the highest dose tested, with exposure levels that were significantly above the recommended clinical dose in psoriasis patients (150 mg SC on Weeks 0 and 4, then every 12 weeks), providing a margin of exposure of approximately 70.

Genotoxicity and Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were conducted with risankizumab. A monoclonal antibody is not expected to cause genotoxicity by either direct interaction with DNA or by affecting chromosomal structure. Therefore, genotoxicity testing was not carried out in line with ICH S6(R1) and this is acceptable.

As risankizumab does not bind rodent IL-23 and lacks pharmacological activity in these species, evaluation of the effect of risankizumab blockade of IL-23 binding to its receptor to influence carcinogenesis was not feasible in these species. Therefore, a weight of evidence approach was undertaken to evaluate the potential malignancy risk of risankizumab for humans.

Data indicate that IL-23 promotes tumorigenesis by inducing inflammatory responses, promoting tissue proliferation, angiogenesis, and suppressing immune surveillance against tumour initiation, progression, elimination and metastasis. Thus, blocking IL-23 by risankizumab may be beneficial in preventing tumour growth. In addition, genetically modified mice lacking IL-23 show a lower incidence of tumours and a longer latency to develop tumours in several chemically induced tumour models. Blocking the IL-23 signaling with anti-IL-23 antibodies in mice or using genetically modified mice was shown to result in reduced growth and/or metastasis of transplanted tumour cell lines.

In the completed toxicology package, no increased risk of malignancy has been observed in toxicology studies with risankizumab. There was no evidence of preneoplastic or neoplastic lesions and there was no evidence of immunosuppression in the chronic 26-week monkey study with subcutaneous (SC) dosing of up to dose levels of 50 mg/kg/week. Furthermore, in clinical trials with dosing of risankizumab for up to 52 weeks, there is to date no evidence for an increased risk of malignancies.

On the basis of the weight of evidence approach in conjunction with the observations in preclinical and clinical studies, the risk of malignancy from dosing with risankizumab is considered to be low.

Reproduction and Developmental toxicity

Reproductive and developmental toxicity assessment was conducted with risankizumab in cynomolgus monkeys. The potential for effects on male and female fertility was assessed by evaluation of the reproductive tract as part of the 26-week chronic toxicity study. There were no effects observed on the female reproductive tract. In 4 of 14 male monkeys, minimal to slight hypospermatogenesis (multifocal reduction in the number of round and elongating spermatids in the affected seminiferous tubules without apparent spermatid degeneration) was observed. Based on this assessment a further 26-week fertility study was undertaken in male cynomolgus monkeys. No risankizumab-related effects occurred for any of the endpoints evaluated, and there were no testis weight differences or gross or microscopic pathology

findings. As there were no adverse effects in the male reproductive study a Pathology Working Group (PWG) reviewed the findings from the first 26-week toxicology study, the originally observed findings were determined following review not to be dose dependent non-adverse hypospermatogenesis, but rather reflected normal testicular development in young peripubertal cynomolgus monkeys. The lack of findings in the second study support the conclusion of the PWG. Male and female fertility in monkeys is therefore not likely to be affected after chronic dosing with risankizumab at doses up to 50 mg/kg/week.

The effects of risankizumab on embryo-foetal as well as on pre- and postnatal development were evaluated in an enhanced pre- and postnatal development (ePPND) toxicity study in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered doses up to 50 mg/kg/week by subcutaneous injection once weekly from Gestation Day (GD) 20 to 22 until parturition for up to 22 doses/animal. Infants were evaluated for growth and development, toxicokinetics and infant immunologic parameters (TDAR and blood lymphocyte subset analysis) for six months post-partum.

Maternal toxicity was not observed and infant growth and development through six months postpartum were unaffected by treatment.

Group-wise differences in foetal/infant losses that were reflected in lower survival were determined to be consistent with the testing laboratory's range of normal outcomes (i.e., historic controls) for ePPND studies in cynomolgus monkeys as well as being consistent with incidence rates reported in scientific literature. It was concluded that risankizumab administration had no effect on foetal/infant survival. The NOAEL for both maternal and developmental outcomes was 50 mg/kg/week, the highest dose administered.

In an enhanced pre- and postnatal toxicity study in cynomolgus monkeys, it was shown that infants were exposed to risankizumab. Although foetal exposure (i.e. during pregnancy) has not been investigated, it is known that in general, IgG antibodies are transported efficiently to the foetus, especially in the last period of gestation (Pentsuk 2009). Risankizumab exposure in infants is attributed to placental transfer, not transfer from milk. It is noted though, that this has not been proven by the applicant, since there are no data from exposure in foetuses nor analyses in milk. However, based on the general knowledge that IgG content in primate milk is low, and immunoglobulins are not absorbed in significant amounts in the gastrointestinal tract of primates, it is agreed that indeed it can be expected that the majority of risankizumab exposure is the result of placental transfer.

In the ePPND study infants were observed for six months post-partum, no dedicated juvenile toxicology studies were carried out and this is acceptable. The ePPND study conducted in cynomolgus monkeys revealed no risankizumab-related effects in infant monkeys up to six months of age. Based on the pharmacology of risankizumab, the toxicity data, including lack of toxicity of the immune system, and as the major organ systems are developed in cynomolgus monkey by 6 months of age and humans by 2 years, this data is considered to sufficiently address the safety profile for all age groups.

Local tolerance

Local tolerance was evaluated during the four-week toxicology study in monkeys for both SC and IV administration. No adverse histopathology findings were identified at either the IV or SC injection site after several injections, indicating that the risk of injection site local irritation due to risankizumab was low.

Other toxicity studies

Antigenicity

Human antibodies are expected to be immunogenic to cynomolgus monkeys, the presence of ADAs did not affect exposure in toxicity studies. Results showed that a substantial portion of total risankizumab was able to bind to target, even in plasma from monkeys that screened ADA positive, indicating that the ADAs

formed in the monkeys did not block the ability of risankizumab to bind to its target and should not affect interpretation of the data.

Immunotoxicity

Administration of risankizumab to cynomolgus monkeys for up to 26 weeks of administration in the repeat dose toxicity study, or in the ePPND study did not produce any adverse signs or perturbation of the immune system. No signs of any clinical infection occurred during the toxicology studies. No adverse changes in haematology or responses to KLH immunization were observed and no adverse microscopic changes were observed in lymphoid tissues. Overall, risankizumab has not demonstrated signs of immunosuppression in the toxicity studies.

Dependence

No dedicated study on abuse liability was conducted; the toxicology studies did not show evidence for abuse potential of risankizumab.

Metabolites

The metabolism of a biological product such as a monoclonal antibody is degradation to small peptides and amino acids using the same metabolic processes as for endogenous proteins. These peptide and amino acids are not expected to trigger any toxicity.

Studies on Impurities

Dedicated purification processes to remove impurities and contaminants have been established instead of conducting preclinical testing for their qualification (ICH S6R1). The drug substance/drug product used in the definitive pharmacology and toxicology studies was comparable to the drug product used for the clinical studies.

Tissue cross reactivity study

Risankizumab was found to bind on extracellular granular material in the placenta. Expression of IL-23 in several placental tissue elements has been described in the literature.

Haemocompatibility

Risankizumab was found, not to induce haemolysis in human whole blood up to a concentration of 2 mg/ml.

Extractables and leachables assessment

For theactive substance, any extractables identified, the potential maximum daily exposure is well below the estimated PDE value indicating that the containers are suitable for the intended use, and that there is no safety hazard to humans regarding leachables.

For thedrug product, no substances of toxicological concern in the simulant extracts were detectable. Only expected organic substances were found in the organic solvent extracts, the overall risk of leachables migrating in the aqueous risankizumab DP formulation is negligible. Also, the daily dose based calculations are a worst case scenario approach, as risankizumab is planned to be dosed quarterly during clinical maintenance.

2.3.5. Ecotoxicity / environmental risk assessment

Risankizumab is an antibody (specifically a monoclonal immunoglobulin), and as such is a protein and a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, risankizumab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The non-clinical pharmacological properties of risankizumab have been adequately characterised. The studies provided have demonstrated that risankizumab has a high affinity for the p19 subunit of both human and cynomolgus monkey IL-23. Risankizumab does not bind human IL-12, it also does not bind rodent IL-23. Risankizumab appears to have higher affinity for the p19 subunit of cynomolgus monkey IL-23 than the human p19 subunit of IL-23, but this may be due to the detection limit of the SPR technology used.

Functionally, *in vitro*, risankizumab inhibits the downstream signaling of IL-23, and IL-17 production in response to human IL-23. In an in vivo mouse ear thickening model, risankizumab inhibits human IL-23-induced ear thickening as well as the induction of tissue IL-17 and IL-22.

Safety pharmacology studies were incorporated into the two GLP repeat dose toxicity studies. Risankizumab did not demonstrate any effect on neurological, respiratory, or cardiovascular function including electrocardiograms, in the four-week and 26-week toxicology studies.

Pharmacokinetics

The pharmacokinetic profile of risankizumab was sufficiently characterized. The pharmacokinetics observed after a single dose was typical of a monoclonal antibody, with low volumes of distribution, low clearance and a long terminal elimination half-life. There were differences observed, however, in the half-life and Cmax values observed after the single dose studies in monkeys compared to humans, and this may be attributed to differences in volume of distribution between monkey and human. It is also noted that the Tmax after IV administration of a dose of 1 mg/kg (10 minutes constant rate infusion) was 2 hours, which although unusual for IV administration may be explained by slow distribution and clearance.

Animals with confirmed ADA positive status were generally only either transiently or intermittently ADA positive during the course of the study. The presence of confirmed positive ADA status did not appear to affect the serum concentrations of risankizumab.

Toxicology

Repeat dose toxicity of risankizumab was evaluated in two GLP studies. For both IV and SC administration the NOAEL was the highest dose tested, 50 mg/kg/week. The risankizumab toxicological assessment conducted in cynomolgus monkey did not identify any toxicologically significant findings in any of the repeat-dose studies. In cynomolgus monkey at the NOAEL of 50 mg/kg/week exposure levels are 69-fold greater than the highest exposure levels in human subjects were observed following SC administration, which is the intended clinical route of administration.

Neither genotoxicity nor carcinogenicity studies were conducted with risankizumab. A monoclonal antibody is not expected to cause genotoxicity by either direct interaction with DNA or by affecting chromosomal structure. On the basis of the weight of evidence approach in conjunction with the observations in preclinical and clinical studies, the risk of malignancy from dosing with risankizumab is considered to be low.

Reproductive and developmental toxicity assessment was conducted with risankizumab in cynomolgus monkeys. Male and female fertility in monkeys is not likely to be affected after chronic dosing with risankizumab at doses up to 50 mg/kg/week. The effects of risankizumab on embryo-foetal as well as on pre- and postnatal development were evaluated in an enhanced pre- and postnatal development (ePPND) toxicity study in cynomolgus monkeys. Maternal toxicity was not observed and infant growth and development through six months postpartum were unaffected by treatment. Six months of age in monkey correlates to approximately 2 years of age in humans. No dedicated juvenile toxicology studies were carried out and this is acceptable. Based on the pharmacology of risankizumab, the toxicity data, including lack of toxicity of the immune system, and as the major organ systems are developed in cynomolgus monkey by 6 months of age and humans by 2 years, this data is considered to sufficiently address the safety profile for all age groups. Also in the ePPND study it was demonstrated that infants were exposed to risankizumab. Risankizumab exposure in infants is attributed to placental transfer, not transfer from milk. It is noted though, that this has not been proven by the applicant, since there are no data from exposure in foetuses, nor analyses in milk. However, based on the general knowledge that IgG content in primate milk is low, and immunoglobulins are not absorbed in significant amounts in the gastrointestinal tract of primates, it is agreed that indeed it can be expected that the majority of risankizumab exposure is the result of placental transfer. Measurable risankizumab concentrations were present in both maternal and fetal plasma up to 91 days post birth.

2.3.7. Conclusion on non-clinical aspects

The provided non-clinical package is considered sufficient to support the marketing authorisation application in psoriasis patients. There are no objections to the approval of risankizumab from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M15-995 (1311.28) 64/ EU, US, Canada, Mexico/ 52 weeks (56 weeks for subjects not enrolling in OLE)	March 2016/ completed/ September 2017/ 491/500	Phase 3, multicenter, randomized, placebo- and active comparator-controlled, double-blind, double dummy, parallel	RZB: 150 mg SC at Wks 0, 4, and q12w UST: 45 mg SC (≤ 100 kg BW) or 90 mg SC (> 100 kg BW) at Wks 0, 4, and q12w PBO: SC Wk 0, 4, then switch to RZB at Wk 16 and q12w	Assess efficacy and safety of RZB compared with PBO and UST in subjects with moderate to severe chronic plaque PsO	RZB: 294/278 UST: 99/91 PBO: 98/ 94 completed Week 16 on placebo; 91 completed study after switching to RZB	336/155 47.0 years (19, 76)	Adults with stable moderate to severe chronic plaque PsO ≥ 6 months; With or without PsA; BSA involvement ≥ 10%; PASI ≥ 12; sPGA ≥ 3; Candidate for systemic or phototherapy; Candidate for ustekinumab	PASI 90 and sPGA clear or almost clear at Wk 16
M16-008 (1311.3) 79/ EU, US, Canada, Japan, Republic of Korea, Australia/ 52 weeks (56 weeks for subjects not enrolling in OLE)	February 2016/ completed, September 2017/ 506/500	Phase 3, multicenter, randomized, placebo- and active comparator-controlled, double-blind, double dummy, parallel	RZB: 150 mg SC at Wks 0, 4, and q12w UST: 45 mg SC (≤ 100 kg BW) or 90 mg SC (> 100 kg BW) at Wks 0, 4, and q12w PBO: SC Wk 0, 4, then switch to RZB at Wk 16 and q12w	Assess efficacy and safety of RZB compared with PBO and UST in subjects with moderate to severe chronic plaque PsO	RZB: 304/289 UST: 100/94 PBO: 102/ 96 completed Wk 16 on placebo; 95 completed study after switching to RZB	361/145 48.0 years (19, 85)	Adults with stable moderate to severe chronic plaque PsO ≥ 6 months; With or without PsA; BSA involvement ≥ 10%; PASI ≥ 12; sPGA ≥ 3; Candidate for systemic or phototherapy; Candidate for ustekinumab	PASI 90 and sPGA clear or almost clear at Wk 16

M15-992 (1311.4) 60/ EU, US, Canada, Japan, Australia, Republic of Korea/ 104 weeks	March 2016/ ongoing/ 507/500	Phase 3, randomized, DB, PBO-controlled. Randomiz-ation stratified by weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1)	RZB: 150 mg SC at Wk 0, 4, and 16. At Wk 28, subjects with sPGA 0 or 1 re-randomized to RZB or PBO, subjects with sPGA ≥ 2 at Week 28 received OL RZB q12w PBO: SC at Wk 0, 4; switch to blinded RZB at Wk 16; at Wk 28, subjects with sPGA 0 or 1 received blinded RZB q12w; subjects with sPGA ≥ 2 received OL RZB q12w Beginning at Week 32, any subject with sPGA ≥ 3 received RZB, loading dose 4 wks later, and q12w	Assess safety and efficacy of RZB compared with PBO in subjects with moderate to severe chronic plaque PsO. Evaluate maintenance of response and response to re-treatment after relapse, following drug withdrawal. In a subset of subjects with PsA, evaluate improvement in signs and symptoms	RZB: 407/14 (363 ongoing at data cut-off) PBO: 100/1 (84 ongoing at data cut-off after switching to RZB)	356/151 51.0 years (19, 80)	Adults with stable moderate to severe chronic plaque PsO ≥ 6 months; With or without PsA; BSA involvement ≥ 10%; PASI ≥ 12; sPGA ≥ 3; Candidate for systemic or phototherapy	PASI 90 and sPGA clear or almost clear at Wk 16
M16-010 (1311.30) 66/ EU, US, Canada, Mexico, Taiwan/ 44 weeks (48 weeks for subjects not enrolling in the OLE)	March 2016 completed, August 2017/ 605/600	Phase 3, active-controlled, double-blind, double dummy, randomized, parallel	RZB: 150 mg SC at Wks 0, 4, and q12w thereafter Adalimumab: SC, 80 mg at Wk 0; 40 mg every other week from Wk 1 to Wk 15; at Wk 16, subjects continued on adalimumab, switched to RZB or were re-randomized to RZB or adalimumab, depending on PASI score.	Assess safety and efficacy of RZB compared with adalimumab in subjects with moderate to severe chronic plaque PsO	RZB: 301/274 Adalimumab: 304/276	422/183 47.0 years (18, 81)	Adults with stable moderate to severe chronic plaque PsO ≥ 6 months; With or without PsA; BSA involvement ≥ 10%; PASI ≥ 12; sPGA ≥ 3; Candidate for systemic or photo therapy; Candidate for adalimumab	PASI 90 and sPGA clear or almost clear at Wk 16

2.4.2. Pharmacokinetics

Introduction

This application is seeking approval for risankizumab for the treatment of moderate to severe chronic plaque psoriasis. The proposed clinical dose is 150 mg administered subcutaneously (SC) at Week 0, Week 4 and every 12 weeks thereafter for all subjects with moderate to severe chronic plaque psoriasis. The to-be-marketed drug product is supplied in a pre-filled syringe containing 75 mg of risankizumab in 0.83 mL (90 mg/mL).

Studies conducted to date that were pertinent to risankizumab pharmacokinetics included a Phase 1 study in healthy subjects (Study M16-513) and a Phase 1 study in subjects with moderate to severe plaque psoriasis (Study 1311.1), to evaluate the pharmacokinetics and immunogenicity, along with safety and tolerability, of risankizumab. The pharmacokinetics, immunogenicity, efficacy and safety of risankizumab were evaluated in one Phase 2 study (Study 1311.2) and four Phase 3 studies (Study M16-008, Study M16-010, Study M15-995 and Study M15-992), in subjects with moderate to severe chronic plaque psoriasis. The therapeutic protein-drug interaction potential for risankizumab was investigated in a Phase 1 study (Study M16-007) in subjects with moderate to severe chronic plaque psoriasis. In addition to these individual studies, population pharmacokinetic analyses were performed using combined data from these Phase 1, 2 and 3 studies to support the overall characterization of the pharmacokinetics of risankizumab.

Pharmacokinetic parameters for risankizumab were determined using non-compartmental pharmacokinetic analysis methods. For the population pharmacokinetic analysis, the risankizumab PK data were analysed using non-linear mixed effects modelling software NONMEM (Version 7.4).

Analytical Methods

Evaluation of free risankizumab in human plasma

An ELISA assay was developed to determine the free concentration of risankizumab in human plasma. In brief, risankizumab is captured by a polyclonal antibody that has been coated on an ELISA plate. Captured drug is then bound by a biotinylated blocking anti-idiotypic risankizumab antibody. The assay was validated for accuracy, precision, linearity, selectivity, specificity, matrix interference, dilutional integrity and sample stability. The defined assay performance specifications and the method validation carried out are, in general, in line with the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 rev.1 corr.2). Queries raised on the evaluation of sample stability and the potential impact of anti-drug antibodies on the performance of the ELISA have been satisfactorily addressed.

Evaluation of cytochrome P450 probe substrates in human plasma

LC-MS/MS bioanalytical methods were developed and validated for the quantitative determination of the cytochrome P450 (CYP450) probe substrates (caffeine, omeprazole, midazolam, warfarin and metoprolol) administered alone or in combination with risankizumab in the drug-drug interaction study (study M16-007 [1311.36]). The assays were validated for accuracy, precision, linearity, selectivity, specificity, matrix interference/effect, matrix factor cross-analyte interference, dilution integrity, recovery, sample stability and carryover (). In general, the method validation was carried out in line with the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 rev.1 corr.2).

Evaluation of anti-Risankizumab antibodies in human plasma

The method is a qualitative electrochemiluminescent (ECL) immunoassay designed to detect anti-Risankizumab antibodies in human plasma. In accordance with the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1), the presence of anti-drug antibodies was evaluated using the recommended three tiered approach: an initial screening assay to identify potentially anti-drug antibody positive samples, a confirmation assay based on competition with exogenously added risankizumab and a determination of the titer of antibodies for confirmed positive samples. There are two versions of the assay however the only modification relates to sample dilution prior to analysis.

The assay controls and system suitability criteria described in the method description meet current required standards and are acceptable. In general, the data presented supports adequate validation of the method in terms of sensitivity, precision, selectivity and stability of samples. although some queries

are raised. Queries relating to the intra- and Inter- assay precision estimates for the screening and confirmatory assays have been addressed. With respect to drug tolerance, the sensitivity of the assay in the presence of drug has been justified with respect to the actual levels of drug in plasma at the time of sampling during the studies. Additional queries raised in relation to the sample stability, robustness/reproducibility and carry-over evaluations for the method have been resolved. In addition, the results of incurred samples reanalysis have been provided.. Further information has been presented in relation to the positive control antibody used during sample analysis.

A number of points for clarification raised in relation to the cut point determinations have been addressed. Adequate justification has been presented for the multiplicative correction factors used during sample analysisand the derivation of these correction factors has been explained.

Evaluation of Risankizumab NAbs in study plasma.

The NAB assay is a cell-based method followed by an ELISA analysis of phospho-STAT3. In brief, Risankizumab causes a reduction in IL-23 dependent phosphorylation of STAT3. The assay detects ADAs that can neutralise this mechanism of action.

While a confirmatory step is normally not included in NAb evaluation, the applicant has confirmed that NAb analysis is only performed on samples already screened and confirmed to be ADA positive.

Population PK analysis

A population PK analysis of risankizumab was conducted using PK data from healthy subjects and subjects with moderate to severe plaque psoriasis, enrolled in seven Phase 1 to 3 clinical trials, who received at least one dose of risankizumab administered IV or SC. Overall, 13,501 risankizumab plasma concentration measurements from 1899 subjects were included in the analyses.

A two-compartment model with a first-order absorption for SC administration and first-order elimination adequately described risankizumab pharmacokinetics. The parameters of the final population pharmacokinetic model were estimated with acceptable precision (%RSE ranging from approximately 2% to 17%). Model evaluation using goodness-of-fit plots, visual predictive checks, and bootstrap analyses indicated that the model described risankizumab pharmacokinetics acceptably well.

Risankizumab clearance and volume of distribution increase as body weight increases, resulting in approximately 30% lower exposure in patients with increased body weight (>100 kg). However, changes in efficacy of risankizumab observed with increased body weight were not considered to be clinically meaningful. Risankizumab clearance was increased in patients with ADA titer ≥128 units, resulting in an estimated 30% decrease in risankizumab exposure. However, changes in efficacy of risankizumab observed in ADA positive patients were not considered to be clinically meaningful. None of the other statistically significant covariates identified had a meaningful impact on risankizumab exposures (risankizumab exposures were well within the default 80 to 125% equivalence boundaries over the range of covariate values observed in subjects with psoriasis).

Table 1: Fixed and random effects parameter estimates for risankizumab final population PK model

Parameter	Population Estimate	%RSE[a]	Bootstrap 95% Confidence Interval
Pharmacokinetic Parameters			
Clearance (CL; L/day)	0.243	1.8	0.217 to 0.263
Central Volume of Distribution (V_c; L)	4.86	3.8	3.95 to 5.53
Absorption Rate Constant (Ka; day^{-1})	0.229	4.8	0.179 to 0.296
Inter-Compartmental Clearance (Q; L/day)	0.656	3.7	0.540 to 0.783
Peripheral Volume of Distribution (V_p; L)	4.25	2.0	3.85 to 4.65
Absolute SC Bioavailability of CMC1 (F)[b]	0.710	11.1	0.624 to 0.781
Absolute SC Bioavailability of CMC2 (F)[c]	0.890	7.2	0.791 to 0.960
Exponent for the Effect of Body Weight on Risankizumab Clearance (CL)	0.933	3.3	0.862 to 0.995
Exponent for the Effect of Body Weight on Risankizumab Central Volume of Distribution (V_c)	1.17	7.2	0.979 to 1.35
Exponent for the Effect of Serum Albumin on Risankizumab Clearance (CL)	–0.715	10.6	–0.886 to –0.516
Exponent for the Effect of Serum Creatinine on Risankizumab Clearance (CL)	–0.253	10.2	–0.308 to –0.203
Exponent for the Effect of C-Reactive Protein on Risankizumab Clearance (CL)	0.044	10.5	0.034 to 0.054
Exponent for the Effect of Body Weight on Risankizumab Peripheral Volume of Distribution (V_p)	0.377	12.0	0.245 to 0.520
Proportional Increase in CL for an ADA titer ≥ 128	0.428	5.1	0.287 to 0.766
Inter-Individual Correlation and Residual Variability			
Variance of Inter-Individual Variability in CL, %CV[d], exponential error model	0.054, 24%	3.6	0.038 to 0.067
Variance of Inter-Individual Variability in V_c, %CV[d], exponential error model	0.110, 34%	6.6	0.052 to 0.158
Variance of Inter-Individual Variability in Ka, %CV[d], exponential error model	0.335, 63%	5.5	0.129 to 0.578
Variance of Inter-Individual Variability in F[e]; additive error model in logit domain	0.492	16.9	0.269 to 0.795
Covariance between IIV CL and IIV V_c, % correlation	0.030, 39%	8.1	–0.003 to 0.051
Variance of Proportional Residual Error, % error	0.036, 19%	0.68	0.033 to 0.039

CL = clearance; Ka = first-order absorption rate constant; Q = inter-compartmental clearance; V_c = central volume of distribution; V_p = peripheral volume of distribution

a. % Relative standard error (%RSE) was estimated as the standard error of the estimate divided by the population estimate multiplied by 100.
b. Estimate was back transformed from the logit scale (estimate on the logit scale was 0.896).
c. Estimate was back transformed from the logit scale (estimate on the logit scale was 2.09).
d. %CV = SQRT[exp(ω2)-1]*100.
e. The estimates are provided in logit domain.

Absorption

The absorption of monoclonal antibodies after SC administration is believed to be primarily mediated through the lymphatic system.

- Bioavailability

In the population pharmacokinetic analysis, risankizumab absolute SC bioavailability was estimated to be 89% for the to-be-marketed Phase 3 clinical regimen. Following SC administration, risankizumab reached peak plasma concentrations between 3 and 14 days after dosing. The population estimate for the absorption rate constant (Ka) was 0.23 day^{-1}.

- Bioequivalence

Risankizumab drug substance was initially generated using a manufacturing process coded as CMC1. CMC1 process batches include the early 10 mg/mL vial for IV administration, and the 90 mg/mL 1 mL pre-filled syringe (PFS) for SC administration, used in Phase 1 and Phase 2 clinical studies. Following a change in the manufacturing process, CMC2 batches were produced for Phase 3 trials. This will be the commercial formulation and process. In addition to change in process, CMC2 batches are presented in a different type (brand) of syringe containing 75 mg of risankizumab in 0.83 mL (90 mg/mL). The comparability between CMC1 batches and CMC2 batches is detailed in Section 3.1 Quality aspects.

Distribution

Monoclonal antibodies are largely confined to the vascular and interstitial spaces and have a small apparent volume of distribution compared to low molecular weight drugs, primarily due to their large molecular size and poor lipophilicity.

Based on population PK modelling, the estimated mean steady-state volume of distribution of risankizumab was approximately 9.1 L in a typical 70 kg patient, and approximately 11.2 L in a typical 90 kg patient, indicating that there was some limited distribution into tissue.

Elimination

The elimination routes of monoclonal antibodies involve proteolysis/catabolism into smaller proteins and peptides inside lysosomes of mainly endothelial cells throughout the body following internalization via either receptor or target-mediated endocytosis or non-specific pinocytosis. As an IgG1 monoclonal antibody, risankizumab is not expected to undergo metabolism by hepatic metabolic enzymes or renal elimination.

Based on population PK modelling the plasma clearance of risankizumab was 0.24 L/day for a typical 70 kg patient and 0.31 L/day for a typical 90 kg patient. Clearance of risankizumab was best described by a linear elimination process. The terminal phase elimination half-life was estimated to be 28 days.

Dose proportionality and time dependency

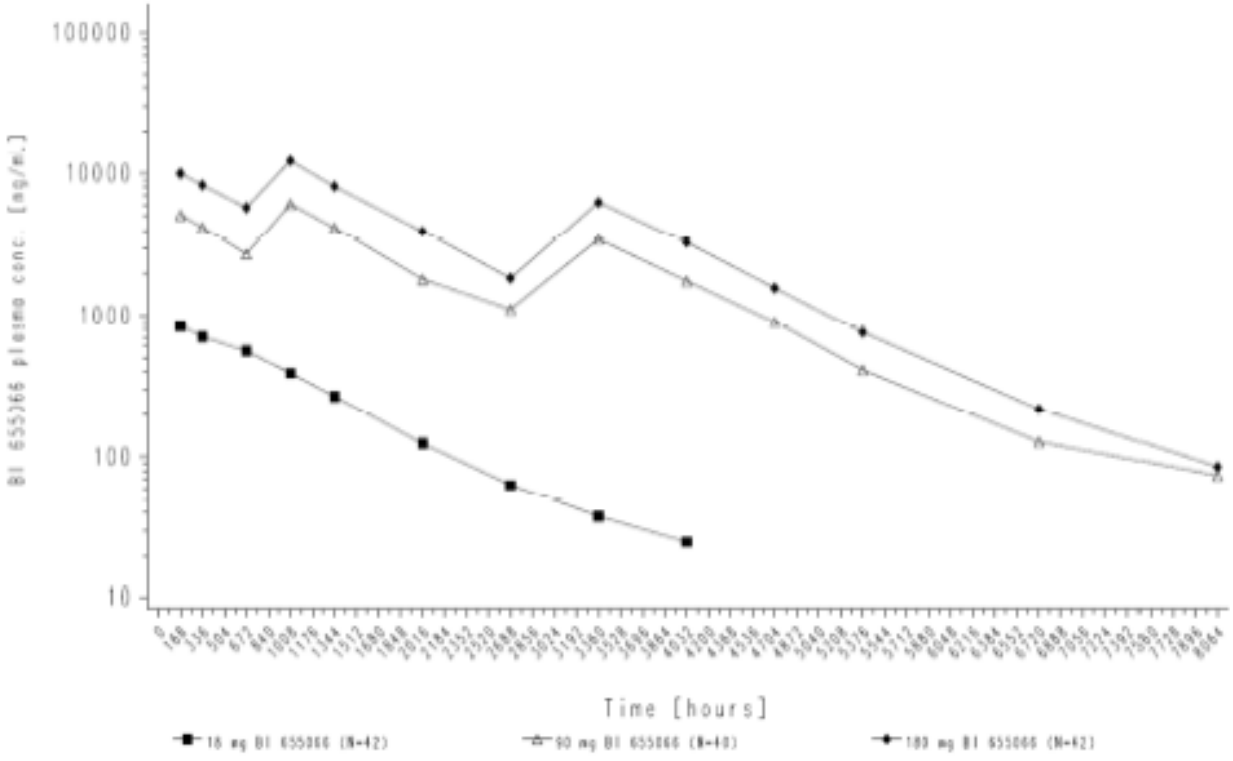
- Dose proportionality

Dose proportionality of risankizumab following SC administration was observed in two Phase 1 trials (Studies 1311.1 and 1311.16) and one Phase 2 trial (1311.2).

Study 1311.1 was a rising single dose trial in patients with moderate to severe plaque psoriasis. Subjects received either a single-dose of risankizumab or matching placebo via IV or SC administration. In patients with psoriasis, single doses of risankizumab from 0.01 mg/kg up to 5 mg/kg IV resulted in dose proportional increases in serum risankizumab exposure, as measured by $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max}. Increases in exposure also appeared to be approximately dose proportional with SC doses of 0.25 mg/kg and 1 mg/kg. However, dose-proportionality at the recommended SC dose of 150 mg cannot be assumed from this study alone.

Study 1311.16 was a rising single dose trial in healthy male subjects. Subjects received either a single-dose of risankizumab or matching placebo via IV or SC administration. Subjects received single doses of risankizumab of 200 mg, 600 mg or 1200 mg IV; or single doses of 18 mg, 80 mg or 300 mg SC. The results indicated that risankizumab exposures across the SC and IV dose ranges were approximately dose proportional.

Study 1311.2 evaluated three risankizumab SC dosing regimens in patients with moderate to severe plaque psoriasis - single (18 mg) or multiple (90 mg and 180 mg) SC injection at weeks 0, 4 and 16. Risankizumab exposure increased in an approximately dose proportional manner across the dose range analysed in this study.



Mean plasma concentration-time profiles of risankizumab after a single (18 mg) or multiple (90 mg and 180 mg) SC injection at weeks 0, 4 and 16.

- Time dependency

Time dependency of risankizumab following SC administration was assessed in four Phase 3 trials (1311.28, 1311.3, 1311.30 and 1311.4), as well as in the population PK analyses.

Across the Phase 3 studies, following SC dosing of risankizumab at the proposed clinical regimen (150 mg at Weeks 0, 4 and every 12 weeks thereafter), the steady-state plasma concentrations of risankizumab in subjects with moderate to severe plaque psoriasis were approximately achieved by Week 16. In the population PK study, based on empirical Bayesian pharmacokinetic parameter estimates, after SC dosing of risankizumab at the proposed clinical regimen, the mean (± SD) model-predicted risankizumab trough plasma concentrations were 2.48 ± 1.35 µg/mL at Week 16, 2.03 ± 1.19 µg/mL at Week 28, and 1.91 ± 1.17 µg/mL at Week 52. These data support the absence of time-dependent behaviour.

Intra- and inter-individual variability

The data from Phase 1, 2 and 3 studies showed moderate to high inter-subject variability of risankizumab after SC dosing, with CV% values on risankizumab exposure ranging from approximately 19% to 89%. In phase 3 studies, there was no clear intra-subject effect of ADAs on risankizumab exposure. In the population PK modelling study, the inter-individual variability (%CV) for risankizumab CL, Vc and Ka parameters were 24%, 34%, and 63%, respectively, and residual variability was 19%.

Table 2: Inter-individual and residual variability for risankizumab parameters in final population PK model

Parameter	Population Estimate	%RSE[a]	Bootstrap 95% Confidence Interval
Inter-Individual Correlation and Residual Variability			
Variance of Inter-Individual Variability in CL, %CV[d], exponential error model	0.054, 24%	3.6	0.038 to 0.067
Variance of Inter-Individual Variability in V_c, %CV[d], exponential error model	0.110, 34%	6.6	0.052 to 0.158
Variance of Inter-Individual Variability in Ka, %CV[d], exponential error model	0.335, 63%	5.5	0.129 to 0.578
Variance of Inter-Individual Variability in F[e]; additive error model in logit domain	0.492	16.9	0.269 to 0.795
Covariance between IIV CL and IIV V_c, % correlation	0.030, 39%	8.1	–0.003 to 0.051
Variance of Proportional Residual Error, % error	0.036, 19%	0.68	0.033 to 0.039

CL = clearance; Ka = first-order absorption rate constant; Q = inter-compartmental clearance; V_c = central volume of distribution; V_p = peripheral volume of distribution

a. % Relative standard error (%RSE) was estimated as the standard error of the estimate divided by the population estimate multiplied by 100.
b. Estimate was back transformed from the logit scale (estimate on the logit scale was 0.896).
c. Estimate was back transformed from the logit scale (estimate on the logit scale was 2.09).
d. %CV = SQRT[exp(ω2)-1]*100.
e. The estimates are provided in logit domain.

Pharmacokinetics in the target population

Based on the population pharmacokinetic model, risankizumab plasma clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp), volume of distribution at steady state (Vss), and terminal phase elimination half-life were estimated to be approximately 0.24 L/day, 4.86 L, 4.25 L, 9.1 L, and 28 days, respectively, for a typical patient 70 kg subject. Risankizumab absolute SC bioavailability was estimated to be 89% for the Phase 3 clinical regimen. Risankizumab PK parameters were not significantly different between healthy volunteers and subjects with psoriasis.

Summary statistics of the model-predicted risankizumab exposures at selected dosing intervals for subjects who participated in the phase 3 trials using the empirical Bayesian individual pharmacokinetic parameter estimates from the final model

Dosing Interval	N	Parameter	Mean (SD)	Median	5th Percentile	95th Percentile
First dosing interval (Weeks 0 – 4)	1198	C_{max} (µg/mL)	10.3 (2.46)	10.3	6.55	14.7
	1198	AUC_{0-4} (µg•day/mL)	217 (56.7)	214	133	314
	1198	C_{trough} (µg/mL)	6.01 (1.86)	5.93	3.15	9.12
Second dosing interval (Weeks 4 – 16)	1184	C_{max} (µg/mL)	15.4 (3.95)	15.2	9.48	22.1
	1184	AUC_{4-16} (µg•day/mL)	622 (208)	608	308	978
	1184	C_{trough} (µg/mL)	2.48 (1.35)	2.28	0.613	4.97
Third dosing interval (Weeks 16 – 28)	1170	C_{max} (µg/mL)	12.4 (3.29)	12.2	7.58	18.0
	1170	AUC_{16-28} (µg•day/mL)	495 (178)	482	234	805
	1170	C_{trough} (µg/mL)	2.03 (1.19)	1.82	0.485	4.21
Fifth dosing interval (Weeks 40 – 52)	740	C_{max} (µg/mL)	11.9 (3.06)	11.8	7.28	17.0
	740	AUC_{40-52} (µg•day/mL)	466 (163)	450	229	750
	740	C_{trough} (µg/mL)	1.91 (1.17)	1.69	0.455	3.99

C_{trough} = plasma concentration at the end of the dosing interval

Special populations

- Impaired renal function

In the population PK analyses, serum creatinine was statistically correlated with risankizumab clearance. However, based on the simulations conducted using the final population pharmacokinetic model, serum creatinine had no significant impact on risankizumab model predicted steady-state Cmax and AUC following the proposed clinical dosing regimen of 150 mg SC at Week 0, 4, and every 12 weeks thereafter, with exposure ratios relative to the reference group being within the default equivalence boundaries of 0.8 to 1.25.

- Impaired hepatic function

In the population PK analyses, hepatic function (bilirubin, ALT and AST), was not significant correlated with risankizumab clearance.

- Gender

In the population PK analyses, gender did not significantly influence risankizumab PK.

- Race

One Phase 1 study [Study M16-513 (1311.16)] was performed, as well as the population pharmacokinetic modelling study, to examine the impact of race on the pharmacokinetics of risankizumab.

In Study 1311.16, after single SC doses of risankizumab 18 mg to 300 mg to healthy Caucasian, Chinese and Japanese subjects, the difference in risankizumab exposure (AUC) in Japanese or Chinese healthy

subjects compared with healthy Caucasian subjects was approximately 30% higher in Japanese subjects and approximately 20% higher in Chinese subjects. After adjusting for bodyweight, risankizumab exposure was comparable across ethnic groups (less than 5% difference), suggesting that exposure differences between ethnicities were driven by bodyweight differences.

In the population PK analyses, race (Asian vs white and other) was not found to be a significant covariate on risankizumab pharmacokinetic parameters.

- Weight

In the population PK analyses, body weight was statistically correlated with risankizumab clearance, central volume of distribution, and peripheral volume of distribution. Based on the simulations conducted using the final population pharmacokinetic model, subjects with bodyweight >100 kg were estimated to have approximately 30% lower risankizumab exposure (Cmax, AUC) than those with bodyweight ≤100 kg. This difference was considered small and not clinically relevant at the proposed clinical regimen (150 mg SC at Weeks 0, 4 and q12w thereafter). Subgroup analyses, comparing PASI 90 and sPGA 0/1 responses at week 1 based on body weight ≤100 kg vs >100 kg using the pooled data across Phase 3 studies in subjects with psoriasis, also suggested that body weight had no impact on risankizumab efficacy. Further, exposure-response analyses indicated that the proposed clinical regimen of risankizumab achieved the plateau of efficacy for the evaluated endpoints (PASI 90, PASI 100 and sPGA 0/1) at Week 16 and Week 52 across the entire body weight range evaluated in subjects with psoriasis.

- Elderly

In the population PK analyses, age (18 to 85 years) was not a statistically significant covariate for risankizumab pharmacokinetic parameters.

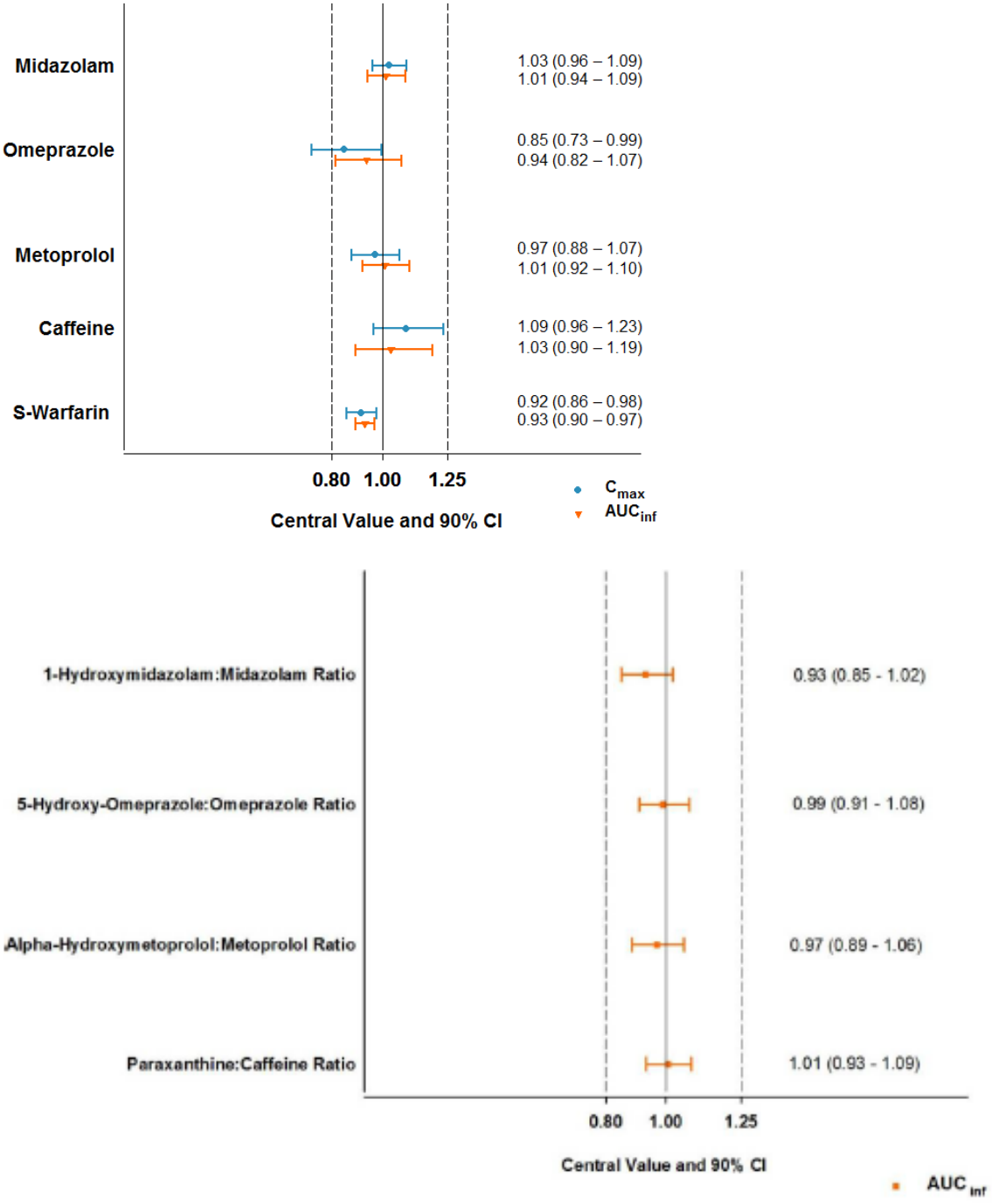
Interactions

The expected consequence of metabolism of biological products is degradation to small peptides and amino acids, the same metabolic processes as for endogenous proteins. As these processes typically have high capacity, they are not likely to be impacted by other co-administered medications. Further, any potential small molecule co-dosed with risankizumab is unlikely to share the same elimination mechanisms as this antibody.

IL-23 plays a key role in the pathophysiology of inflammatory diseases through induction and maintenance of Th17 type cells that secrete inflammatory cytokines. Inhibition of IL-23 by risankizumab in patients may suppress directly or indirectly the pathophysiological expression of downstream cytokines, like IL-17, IL-6, IL-10, IFN-γ and TNF-α (Gaffen et al, 2014). Some of these cytokines are known to impact the expression and stability of various cytochrome P450 (CYP) enzyme isoform (Lee et al, 2010).

In a clinical drug interaction study [Study M16-007 (1311.36)], risankizumab was shown to have a low potential for drug-drug interactions. In this trial, repeated administration of risankizumab 150 mg SC every 4 weeks had no effect on the exposures of probe substrates of CYP1A2 (caffeine 100 mg), CYP2C9 (warfarin 10 mg), CYP2C19 (omeprazole 20 mg), CYP2D6 (metoprolol 50 mg) and CYP3A (midazolam 2 mg) in subjects with plaque psoriasis. The 90% confidence intervals for the ratios of the probe substrates Cmax, AUC0-t, and AUC0-∞, when administered 6 days following the fourth dose of risankizumab 150 mg SC every 4 weeks versus when these substrates were administered prior to initiating risankizumab treatment, were within the default no-effect boundaries of 0.8 to 1.25 (with exception of the lower 90% confidence bound for omeprazole Cmax ratio which extended slightly below 0.8). Consistent with these results, risankizumab had no effect on evaluated metabolite-to-parent AUC ratios for these probe substrates.

Point estimate and 90% confidence intervals for the effect of risankizumab on pharmacokinetic parameters of CYP cocktail substrates (top) and on the metabolite-to-parent drug AUC ratios (bottom).



Immunogenicity

Development of anti-risankizumab antibodies was measured throughout the clinical program. Overall, across Phase 3 studies, the incidence of treatment-emergent ADAs following risankizumab SC treatment was <30% and, in general, approximately half of these ADA-positive subjects were positive for neutralizing antidrug antibodies. Most ADA-positive subjects had relatively low ADA titers (<5 units), with a low proportion having titers >100 units. Comparisons of mean risankizumab concentrations in ADA-positive vs ADA-negative subjects did not show a clear impact of ADAs on risankizumab plasma exposures.

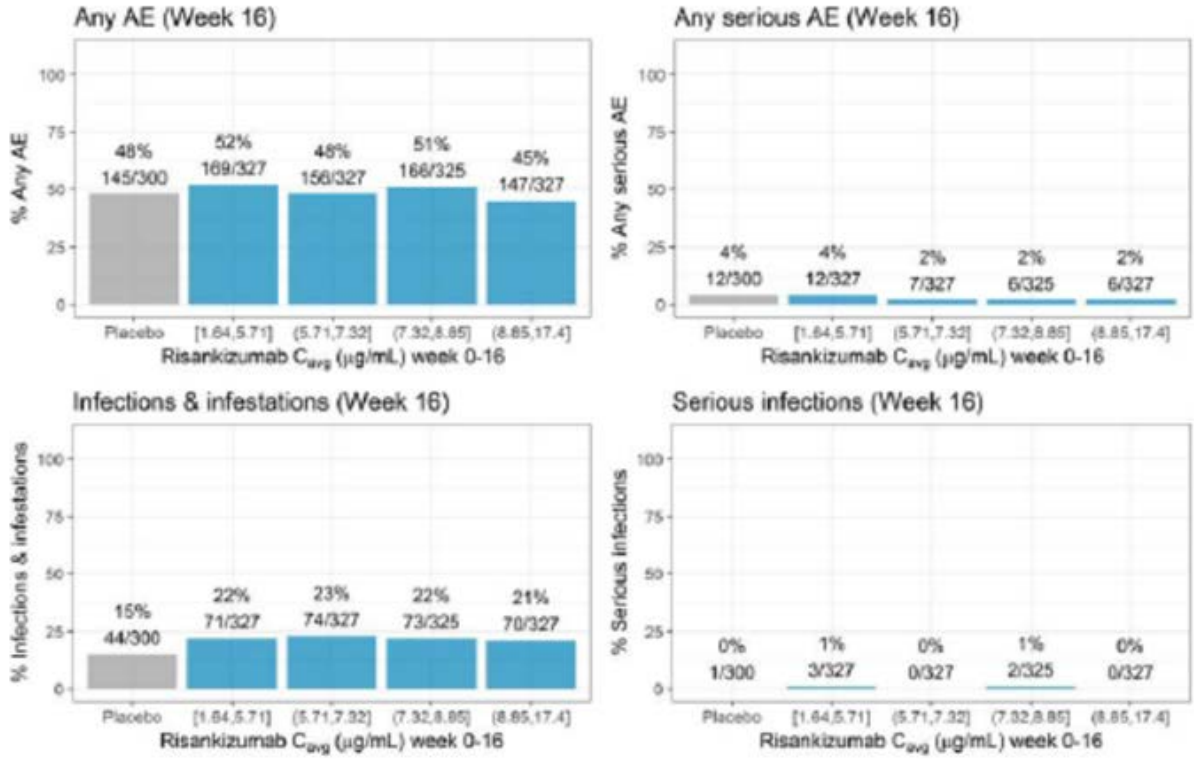
In the population pharmacokinetic analyses of risankizumab data, using data from Phase 2 and 3 clinical trials, ADA titer was significantly correlated with clearance. Anti-risankizumab antibodies did not have any impact on risankizumab clearance in the majority of ADA positive subjects. In a small subset of subjects (28/1807 ADA-positive subjects representing 1.5% of ADA-evaluable subjects in Phase 2 and Phase 3 studies) who developed ADA titer ≥ 128 units, risankizumab clearance was estimated to increase by 43%, resulting in an estimated 30% decrease in risankizumab AUC, on average. This small difference in exposure was considered to be not clinically relevant for the short-term efficacy (Week 16) or long-term (Week 52) maintenance of efficacy (PASI 90 and sPGA 0/1) as confirmed by subgroup analyses for ADA positive subjects versus ADA negative subjects in Phase 3 trials. Presence of neutralizing antibodies (NAb) to risankizumab was not correlated with risankizumab clearance.

Exposure relevant for safety

The exposure-response relationships for safety were performed using pooled data from subjects who received at least one dose of risankizumab across the four Phase 3 studies. The exposure-response relationships were explored for the safety events in relevant areas of interest (any adverse event [AE], serious adverse event [SAE], infection and serious infection) through the first 16 weeks (Week 0 – 16; placebo-controlled period) as well as through the first 52 weeks (Week 0 – 52 for Study M16-008 [1311.3], Study M15-995 [1311.28] and Study M15-992 [1311.4]) and Week 0 – 44 for Study M16-010 [1311.30]).

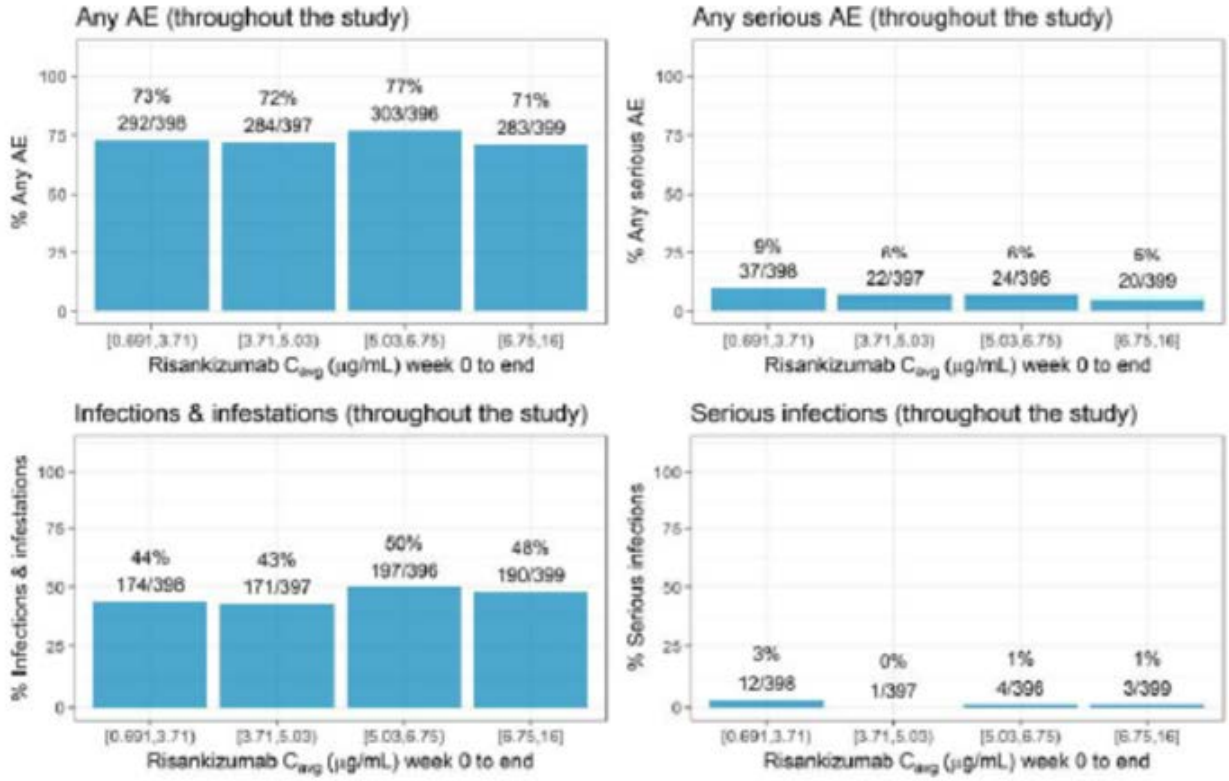
As shown in Figure 11 and Figure 12 (below), there was no apparent relationship between risankizumab exposure and any AE, SAE, infection and infestation or serious infection over the first 16 weeks and up to 52 weeks duration.

Figure 11. **Exposure-Response Relationships Between Risankizumab Plasma C_{avg} and Safety Events of Interest Over the First 16 Weeks (Week 0 – 16)**



Median of average concentrations (Week 0 to 16) (µg/mL): Quartile 1 = 4.76 µg/mL, Quartile 2 = 6.57 µg/mL, Quartile 3 = 8.02 µg/mL, Quartile 4 = 10.13 µg/mL.

Figure 12. Exposure-Response Relationships Between Risankizumab Plasma C_{avg} and Safety Events of Interest Over the First 52 Weeks (Week 0 – 52)



Median of average concentrations (Week 0 to 52) (µg/mL): Quartile 1 = 2.98 µg/mL, Quartile 2 = 4.25 µg/mL, Quartile 3 = 5.87 µg/mL, Quartile 4 = 7.93 µg/mL.

Conclusion

The pharmacokinetics of risankizumab were studied and characterised sufficiently. Important issues arising from the population PK study including the impact of body weight and ADA status on clinical response have been resolved.

2.4.3. Pharmacodynamics

Mechanism of action

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor complex. IL-23 is up-regulated in lesional skin in comparison to non-lesional skin of patients with plaque psoriasis. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Primary pharmacodynamic studies

Primary pharmacology

The exploratory assessment of pharmacodynamic and disease biomarkers in skin biopsies and plasma samples were performed following administration of single dose of risankizumab in the Phase 1 study in

subjects with moderate to severe plaque psoriasis (Study 1311.1). Consistent with the mechanism of action of inhibiting IL-23 binding to its receptor and subsequently the downstream signaling, treatment with risankizumab resulted in decrease in the transcriptomic and protein biomarkers associated with IL 23/IL-17 axis in both plasma and psoriatic skin lesions in subjects with moderate to severe psoriasis compared to placebo.

Following single doses of risankizumab, genes associated with the IL-23/IL-17 axis (IL-23A, IL-22, IL-22RA1, IL-22RA2, IL-17A, IL-17F, IL-17RA, IL-17RC), epidermal hyperplasia and tissue inflammation (β-defensin 2, neutrophil gelatinase lipocalin, and S-100A7/A8), keratinocyte and epithelial cell differentiation (late cornified envelope protein, transglutaminase 1, and cornifelin) were significantly downregulated in lesional skin biopsy samples compared with placebo. Additionally, immunohistochemistry analysis showed that treatment with risankizumab also resulted in decrease in biomarkers associated with thickening of the keratinocyte layer and hyperproliferation, dermal infiltration by T-cells, neutrophils, dendritic cells, and markers of epidermal hyperplasia and tissue inflammation in psoriatic skin lesions. The levels of β-defensin 2, a surrogate marker for disease activity in psoriasis, in plasma were decreased after treatment with risankizumab compared with placebo at multiple time points.

Secondary pharmacodynamic studies

Secondary pharmacology

A thorough QT study with risankizumab was not conducted. In the Scientific Advice in October 2015, CHMP agreed that a thorough QT study with risankizumab was not required.

Safety pharmacology programme

Pharmacodynamic interactions with other medicinal products or substances

No clinical studies were conducted.

Genetic differences in PD response

No information was provided.

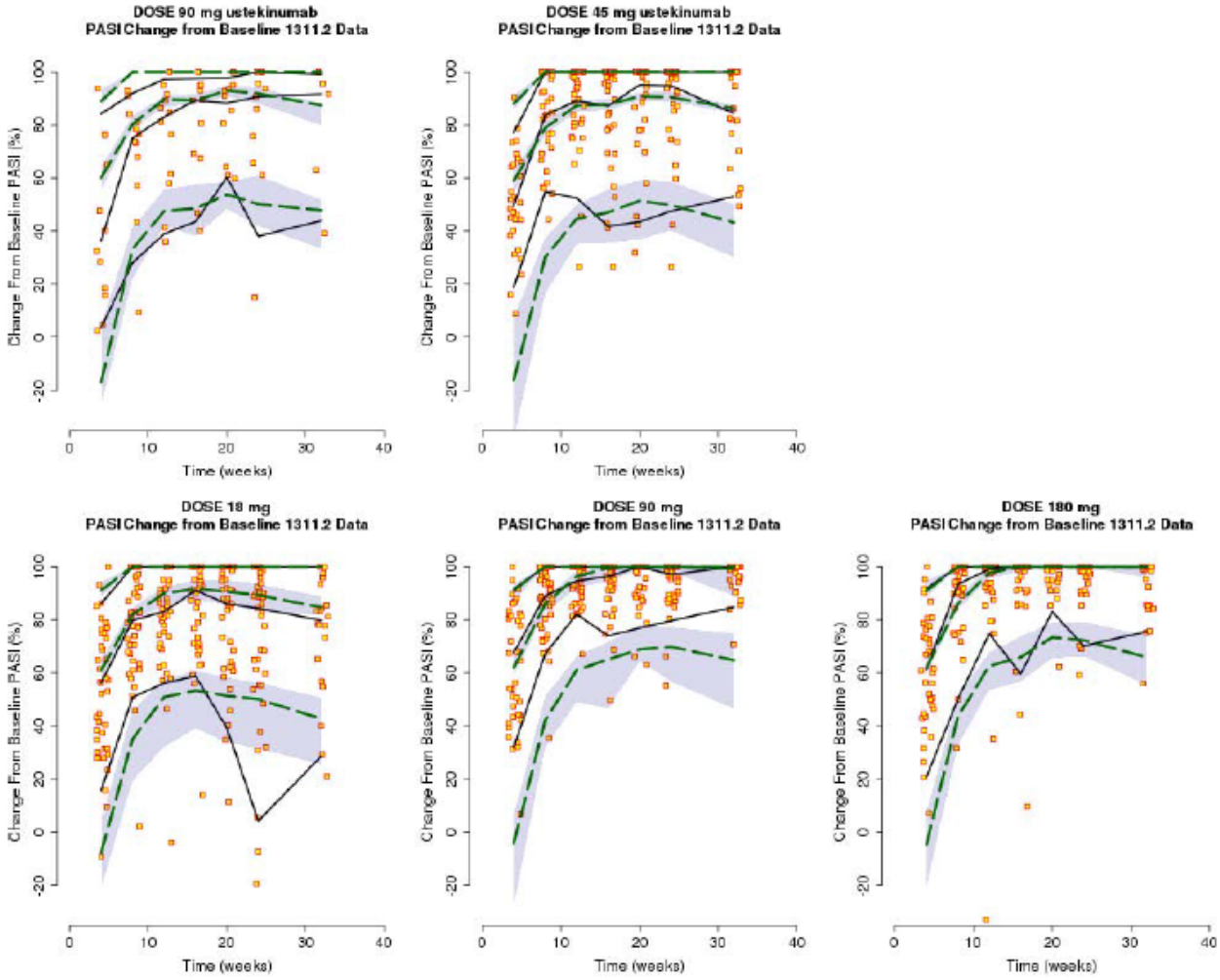
Relationship between plasma concentration and effect

The PK-PD study was based on all available pharmacokinetic data from the completed Phase 1 study (1311.1) and data through at least week 12 from all subjects receiving risankizumab in the ongoing Phase 2 study (1311.2). A sequential exposure-response modelling approach was used to fit the PK (plasma concentration-time) and PD (PASI score-time) of risankizumab in subjects with psoriasis. PK parameters were obtained from a population PK model developed for risankizumab. The response (PD effect) was the reduction in PASI score by inhibiting the formation of psoriatic skin plaques.

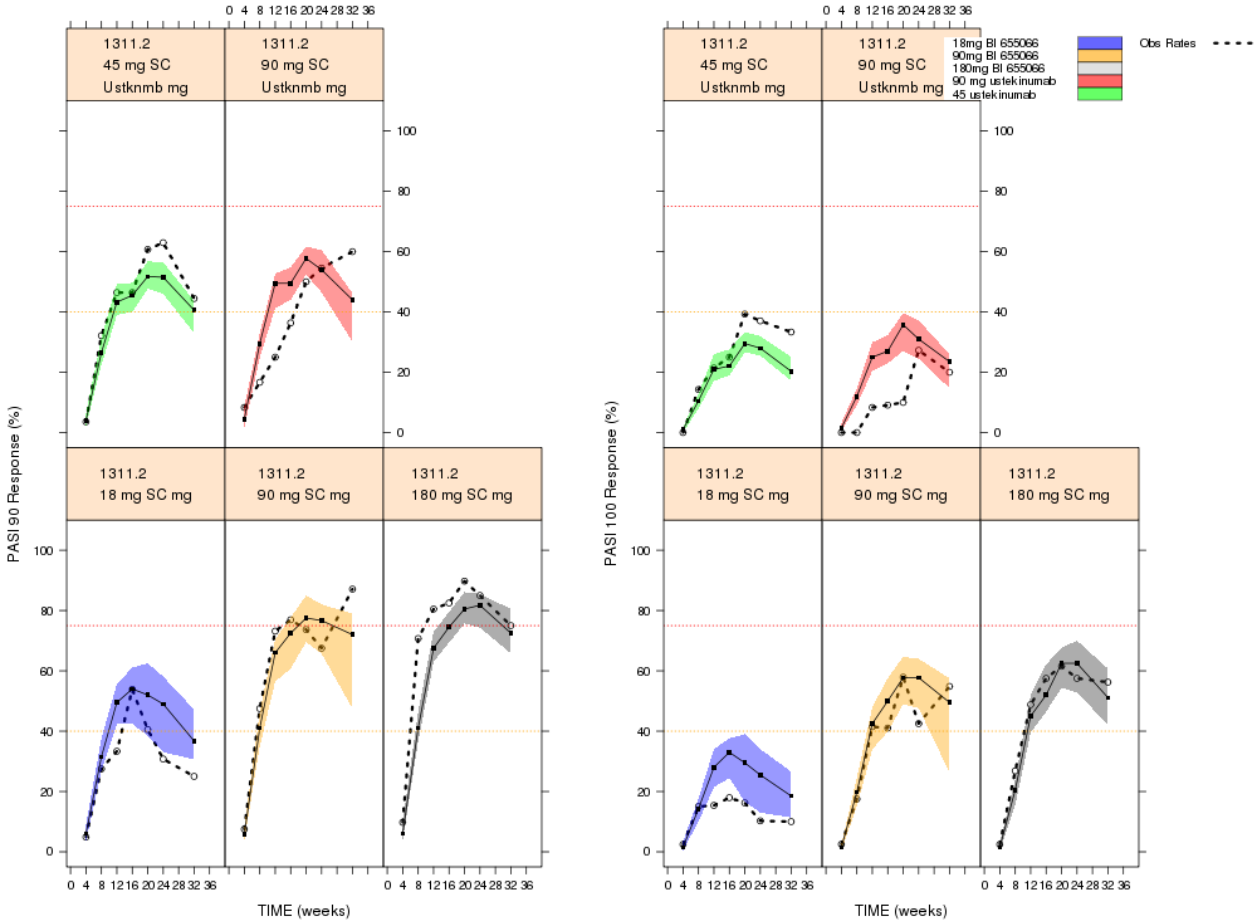
Table 3:Structural (fixed effect) and variance (random effect) parameters of the current population risankizumab PK-PD model of PASI data.

θ/ ω^2	Parameter	Units	EST	SE	RSE (%)	CV IIV (%)	Description
1	baseline	[-]	-1.01	0.05	4.73		rescaled PASI baseline- logit scale
2	kout	[-]	0.04	0.00	2.19		fractional first-order rate constant
3	IC50	[ng/ml]	0.51	0.05	10.1		concentration at 50% of maximum PASI inhibition
4	Imax	[-]	1.90	0.24	12.6		maximal inhibition of PASI
5	Hill coef.	[-]	0.20	0.03	14.4		power coefficient for the Emax relationship
6	tau	[-]	27.1	0.46	1.68		beta reg. dispersion parameter
7	kPLB	[-]	0.47	0.10	22.1		maximum placebo effect
8	gamma1	[-]	2.86	0.04	1.50		augmented distribution param. 1
9	gamma0	[-]	1.69	0.05	2.69		augmented distribution param. 2
10	Uste Offset	[-]	1.83	0.21	11.3		ustekinumab IC50 offset param
1	$\omega^2_{(1,1)}$	[-]	0.19	0.02	12.42	43.2	Random effect baseline PASI

EST= estimate; RSE= relative standard error; SE= standard error, Θ fixed effects parameters, ω^2 random effects parameters



Change from Baseline PASI Visual Predictive Check using the PASI PK-PD model. Orange points represent observed PASI response and black lines the observed 5th, 50th and 95th percentiles of PASI across time for dose groups of Study 1311.2. 90% prediction intervals for the corresponding 5th, 50th and 95th intervals were constructed taking into account between subject variability.



PASI 90 and PASI100 response rates Visual Predictive check using the current PASI PK-PD model. Black dashed line represents the observed PASI 90 or PASI100 response rates. Polygons were constructed to include 90% of simulated response rates from 200 simulations of the original dataset, taking into account between subject variability.

2.4.4. Results of predictions (simulations) with the PK-PD model of PASI scores for a range of doses and regimens is detailed and discussed in the Clinical efficacy section .Discussion on clinical pharmacology

The proposed clinical dose is 150 mg risankizumab SC at Week 0, Week 4, and every 12 weeks thereafter, which has been used in four Phase 3 studies. The administration routes in the clinical studies of risankizumab were SC and/or IV.

Pharmacokinetics

The pharmacokinetics was studied in healthy volunteers and patients with psoriasis. Non-compartmental PK analysis was conducted in studies with intensive PK data and some with sparser PK data. A population pharmacokinetic model was developed to identify patient-specific factors that may explain pharmacokinetic variability of risankizumab.

Population PK modelling

Data from seven studies were used for population PK modelling. Risankizumab PK, after single or multiple administrations through IV or SC routes in healthy subjects or subjects with psoriasis, was adequately described by a 2-compartment PK model with linear absorption after SC administration and linear elimination from the central compartment.

Risankizumab clearance and volume of distribution increase as body weight increases resulting in reduced exposure in patients with increased body weight (>100 kg). However, changes in efficacy of risankizumab observed with increased body weight were not considered to be clinically meaningful. Risankizumab clearance was increased in patients with ADA titer ≥128 units. However, changes in efficacy of risankizumab observed in ADA positive patients were not considered to be clinically meaningful. None of the other statistically significant covariates identified had a meaningful impact on risankizumab exposures.

Bioavailability

Following SC administration, risankizumab reached peak plasma concentrations between 3 and 14 days after dosing with absolute bioavailability estimated to be 89% based on cross-study population pharmacokinetic analyses, which is consistent with results from non-compartmental analysis. The population estimate for Ka was 0.23 day^{-1}. 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.

Distribution

Monoclonal antibodies are largely confined to the vascular and interstitial spaces and have a small apparent volume of distribution compared to low molecular weight drugs, primarily due to their large molecular size and poor lipophilicity.

Based on population PK modeling, the estimated mean steady-state volume of distribution of risankizumab was approximately 9.1 L in a typical 70 kg patient, and approximately 11.2 L in a typical 90 kg patient, indicating that there was some limited distribution into tissue.

Elimination

The elimination routes of monoclonal antibodies involve proteolysis/catabolism into smaller proteins and peptides inside lysosomes of mainly endothelial cells throughout the body following internalization via either receptor or target-mediated endocytosis or non-specific pinocytosis. As an IgG1 monoclonal antibody, risankizumab is not expected to undergo metabolism by hepatic metabolic enzymes or renal elimination.

Based on population PK modelling, the plasma clearance of risankizumab was 0.24 L/day for a typical 70 kg patient and 0.31 L/day for a typical 90 kg patient. Clearance of risankizumab was best described by a linear elimination process. The terminal phase elimination half-life was estimated to be 28 days.

Dose proportionality and time dependency

The pharmacokinetics of risankizumab appeared to be 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.

Intra- and inter-individual variability

In phase 3 studies, there was no clear intra-subject effect of ADAs on risankizumab exposure. The data from Phase 1, 2 and 3 studies indicate that inter-subject variability (CV%) of risankizumab after SC

administration is moderate to high, with CV% values on risankizumab exposure ranging from approximately 19% to 89%. In the population PK modelling, the estimates of inter-individual variability (CV%) for CL, Vc and Ka were 24%, 34%, and 63%, respectively.

Pharmacokinetics in the target population

Based on the population pharmacokinetic model, risankizumab plasma clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp), volume of distribution at steady state (Vss), and terminal phase elimination half-life were estimated to be approximately 0.24 L/day, 4.86 L, 4.25 L, 9.1 L, and 28 days, respectively, for a typical patient 70 kg subject. Risankizumab absolute SC bioavailability was estimated to be 89% for the Phase 3 clinical regimen. Risankizumab PK parameters were not significantly different between healthy volunteers and subjects with psoriasis.

Special populations

Renal function (serum creatinine, creatinine clearance), hepatic function (ALT, AST, bilirubin), gender, race (Asian vs white and other), age (18 to 85 years), disease category (healthy vs psoriasis patient), concomitant medications used in Phase 3 studies, as well as NAb, did not appear to significantly affect exposure to risankizumab. Exposure to risankizumab is decreased in patients with increased body weight and in patients with high ADA titer. However, clinically meaningful changes in efficacy of risankizumab were not observed in patients with increased body weight or in ADA positive patients.

Body weight was significantly correlated with risankizumab clearance. Subjects with body weight > 100 kg were estimated to have approximately 30% lower risankizumab exposure than subjects with body weight ≤ 100 kg. However, this difference in exposure was considered not clinically relevant at the clinical regimen (150 mg SC at Weeks 0, 4 and q12w thereafter), since body weight had minimal impact on risankizumab efficacy as assessed by the PASI 90 and sPGA of clear or almost clear responses.

Anti-drug antibodies (anti-risankizumab antibodies) did not have any impact on risankizumab clearance in the majority of anti-drug antibody positive subjects. Only ADA titers of at least 128 were found to have any impact on risankizumab clearance. In the small subset of subjects who developed ADA titer ≥ 128 (28/1807; representing 1.5% of anti-drug antibody evaluable subjects in Phase 2 and Phase 3 studies), risankizumab clearance was estimated to increase by 43%, resulting in approximately 30% decrease in risankizumab AUC on average. This difference in exposure was shown to be not clinically relevant for the short-term efficacy (Week 16) or long-term (Week 52) maintenance of efficacy (PASI 90 and sPGA of clear or almost clear) as confirmed by subgroup analyses for anti-drug antibody positive versus negative subjects in Phase 3 trials.

Interactions

Risankizumab was shown to have a low potential for drug-drug interactions. In a clinical drug interaction study, repeated administration of risankizumab 150 mg SC every 4 weeks had no effect on the exposures of probe substrates of CYP1A2 (caffeine 100 mg), CYP2C9 (warfarin 10 mg), CYP2C19 (omeprazole 20 mg), CYP2D6 (metoprolol 50 mg) and CYP3A (midazolam 2 mg) in subjects with plaque psoriasis. The 90% confidence intervals for the ratios of the probe substrates Cmax, AUC0-t, and AUC0-∞, when administered 6 days following the fourth dose of risankizumab 150 mg SC every 4 weeks versus when these substrates were administered prior to initiating risankizumab treatment, were within the default no-effect boundaries of 0.8 to 1.25 (with exception of the lower 90% confidence bound for omeprazole Cmax ratio which extended slightly below 0.8). Consistent with these results, risankizumab had no effect on evaluated metabolite-to-parent AUC ratios for these probe substrates.

Immunogenicity

Development of anti-risankizumab antibodies was measured throughout the clinical program. Overall, across Phase 3 studies, the incidence of treatment-emergent ADAs following risankizumab SC treatment

was <30% and, in general, approximately half of these ADA-positive subjects were positive for neutralizing antidrug antibodies. Most ADA-positive subjects had relatively low ADA titers (<5 units), with a low proportion having titers >100 units. Comparisons of mean risankizumab concentrations in ADA-positive vs ADA-negative subjects did not show a clear impact of ADAs on risankizumab plasma exposures.

In the population pharmacokinetic analyses of risankizumab data, using data from Phase 2 and 3 clinical trials, ADA titer was significantly correlated with clearance. In ADA-positive subjects with ADA titers of 128 or higher, on average, risankizumab AUC decreased by 30%. However, in subgroup analysis, it was shown that this reduction in exposure was not clinically relevant for the short-term efficacy or long-term maintenance of efficacy, which is accepted.

Exposure relevant to safety

There was no apparent relationship between risankizumab exposure and any AE, SAE, infection and infestation or serious infection over the first 16 weeks and up to 52 weeks duration using pooled data from all four Phase 3 studies of risankizumab in subjects with moderate to severe plaque psoriasis.

Pharmacodynamics

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor complex. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Primary pharmacology

The exploratory assessment of pharmacodynamic and disease biomarkers in skin biopsies and plasma samples were performed following administration of single dose of risankizumab in the Phase 1 study in subjects with moderate to severe plaque psoriasis. Consistent with the mechanism of action of inhibiting IL-23 binding to its receptor and subsequently the downstream signaling, treatment with risankizumab resulted in decrease in the transcriptomic and protein biomarkers associated with IL 23/IL-17 axis in both plasma and psoriatic skin lesions in subjects with moderate to severe psoriasis compared to placebo.

Relationship with plasma risankizumab concentration and effect

The PK-PD study was based on all available pharmacokinetic data from the completed Phase 1 study (1311.1) and data through at least week 12 from all subjects receiving risankizumab in the ongoing Phase 2 study (1311.2). A sequential exposure-response modelling approach was used to fit the PK (plasma concentration-time) and PD (PASI score-time) of risankizumab in subjects with psoriasis. PK parameters were obtained from the population PK model developed for risankizumab. The response (PD effect) was the reduction in PASI score by inhibiting the formation of psoriatic skin plaques.

A semi-mechanistic PK/PD model describing the relationship with plasma risankizumab concentrations and PASI response over time was developed. The time course of PASI response was modelled using the indirect response PK-PD modeling approach, which is appropriate for these types of data. Modelling indicated a clear exposure-response relationship. Model parameters were estimated with acceptable precision. Inter-patient variability of parameters was moderate. In general, the goodness of fit plots showed that the PK-PD model was able to adequately predict PASI time-course data.

An important issue arising from the PK-PD study (as well as the population PK study) was the potential impact of body weight on clinical response. Additional data provided by the applicant showed that PASI responses seem to be consistent across different weight categories up to 130 kg, but not above. This observation is in line with the assumption that the plasma levels are mostly on the plateaux of the concentration-effect curve. However, the concentration-effect curve is quite steep, and even a small decrease of Cavg concentration may lead to a substantial efficacy loss. At Cavg levels below 2.5 - 3 µg/mL, the efficacy loss steeply accelerates, and the mean concentration of obese patients (> 130 kg) is at this critical level. Therefore, about 50% of this obese patient population had concentrations below the critical level. Body weight tiered dosing does not seem to be a realistic and useful alternative. The SmPC was amended to inform about lesser efficacy in patients with body weight above 130 kg. This has been implemented.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of risankizumab were well studied and characterised. No major objections were raised in terms of clinical pharmacology for this application. The applicant has responded adequately to all concerns.

2.5. Clinical efficacy

The recommended dose and dosing regimen used in the Phase 3 studies were selected based on the safety, efficacy and pharmacokinetic data from the Phase 1 (Study 1311.1) and Phase 2 (Study 1311.2) studies in adult patients with plaque psoriasis, formulation considerations, patient acceptability considerations, as well as exposure-response analyses.

In phase I first-in-human single dose study (study 1311.1), at doses of 0.25 mg/kg (~19 mg for 75 kg patient), 1, 3, and 5 mg/kg (~375 mg for 75 kg patient) by IV or SC administration, all active dose groups showed improvement in mean PASI scores at 24 week follow-up with doses > 1 mg/kg showing near maximal PASI reduction.

2.5.1. Dose response study

For the phase II dose ranging study (Study 1311.2) 3 doses were selected e.g mg 18 SC single dose at Week 0, and 90 and 180 mg SC multiple doses at Weeks 0, 4, and 16. In this study the dose-response was evaluated on outcomes such as PASI responder rates at 90% at week 12 (primary endpoint), 75, 50 and 100% levels, PGA scores and DLQ index. This is in line with the EMA psoriasis Guideline that recommends using a global psoriasis endpoint along with PASI response.

The selected study population was compatible with the patient population in the pivotal studies and representative of the target population.

In this study, overall, best results were obtained for 90mg and 180 mg dose as compared to 18 mg for which a significant difference as compared to Stelara was not seen for most endpoints.

For doses 90 mg and 180 dose mixed efficacy results were reported. Both 90mg and 180 mg doses were superior as compared to Stelara for PASI 90 at Week 12 but not for PASI 90 at Week 24 as at this time point only 180 mg dose was better to Stelara. On the other hand for PASI75 at Week 12 only 90mg dose was superior to Stelara.

For pivotal studies 150 mg dose was selected. In line with the SmPC the recommended dose is 150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

The 150 mg dose and dosing regimens (e.g Week 0, Week 4, and every 12 weeks thereafter) was selected based on the results of the Population Pharmacokinetic and Exposure-Response Analyses of Risankizumab from Phase 1 and 2 Studies in Subjects with Psoriasis which included data from phase I (study 1311.1) and phase II study (study 1311.2). It can be noted that the proposed dosage regimen is the same as the posology approved for Stelara (ustekinumab), with the same target (IL-23) and with a similar half-life as risankuzumab (approximately 3 weeks).

Under the proposed regimen, doses of 150 mg are predicted to result in near maximal PASI 90 and PASI 100 rates; additional increases in dose of risankuzumab up to two-fold (300 mg) are predicted to result in no more than a 5% increase in PASI 90 response rates.

In addition alternative dosing regimens were investigated in this PK/PD analysis. Based on PK-PD considerations alone, the 0, week4 q8 regime offers only minimal advantages over q12 while for q16 decreased efficacy was observed. It is noted that the predicated time to the first loss of PASI 90 response for doses >90 mg was long e.g > 300 days.

It is known that patients with psoriasis tend to be overweight or obese. Some of the biological products approved for use in psoriasis have a weight-based posology (Remicade, Stelara), while others don´t (e.g. Humira, Enbrel and Cosentyx). For Stelara (ustekinumab), a cut-off is applied, with patients weighing >100 kg receiving the double dose. The applicant claims that the weight-based posology is not required as the predicted median response rates for PASI 90 and PASI 100 would only differ by about 5% for a body weight of 60 kg vs. 120 kg based on the PASI PK-PD model. For subjects with body weight >130kg information has been included to inform about lesser efficacy. However no dose adjustment is considered necessary**.**

2.5.2. Main studies

2.5.2.1. Study M15-995 (1311.28) and M16-008 (1311.3)

Studies Risankizumab/Protocol M15-995 and Risankizumab/Protocol M16-008 were of the same design and therefore are presented and discussed together.

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 pharmacokinetics (PK) and the emergence of anti-drug antibodies (ADA) and their effect on efficacy and safety.

- **Methods/study design**

Both studies were Phase 3, multi-center, multi-national, randomized, 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.

The co-primary efficacy endpoints were evaluated at Week 16. Additional endpoints were evaluated at Week 12, 16 and 52.

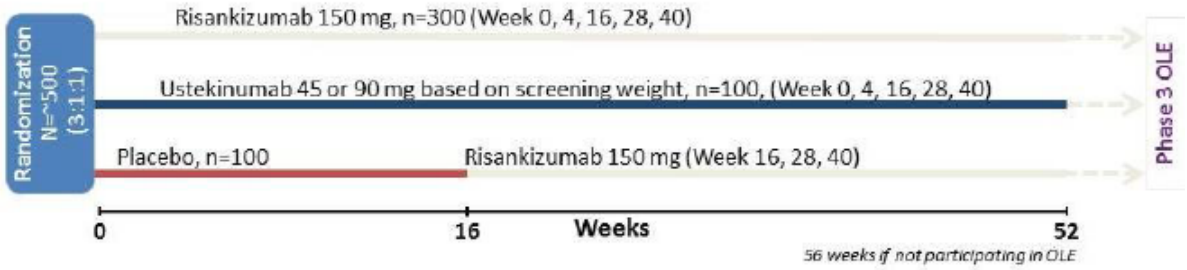
Approximately 500 subjects with moderate to severe chronic plaque psoriasis were planned for this study. Subjects who failed screening were not to be re-screened.

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.

Study Design Schematic for both studies



OLE = open-label extension

- **Study participants**

Main inclusion criteria

- Age ≥ 18 years at screening taking appropriate medication.
- Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient.
- Have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline (Randomisation):
  a) Have an involved BSA ≥ 10% and
  b) Have a PASI score ≥ 12 and
  c) Have a sPGA score of ≥ 3.
- Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator
- Must be a candidate for treatment with Stelara® (ustekinumab) according to local label

Main exclusion criteria

- Patients with
  a) non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular)
  b) current drug-induced psoriasis (including an exacerbation of psoriasis frombeta blockers, calcium channel blockers, or lithium)
  c) active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to investigator's judgment
- Previous exposure to risankuzumab

- Currently enrolled in another investigational study or less than 30 days (from screening) since completing another investigational study (participation in observational studies is permitted)
- Previous exposure to ustekinumab (Stelara®)
- Use of any restricted medication as specified or any drug considered likely to interfere with the safe conduct of the study
- Known chronic or relevant acute infections including active tuberculosis, HIV or viral hepatitis
- Others: Surgery within 12 months, documented or suspected malignancy, history allergy/hypersensitivity, pregnancy or planned pregnancy

- **Treatments**

Risankizumab, ustekinumab, and matching placebos to both risankizumab and ustekinumab were to be administered in the study. Risankizumab 150 mg for subcutaneous (SC) administration was to be provided in 2 prefilled syringes (PFS) of 75 mg each. The dose of ustekinumab was to be administered according to the product's prescribing information. Placebo was also to be administered subcutaneously via a PFS.

Injections were to be given in a double blind/dummy fashion with each patient receiving 2 injections of risankuzumab or matching placebo and 1 injection of ustekinumab or matching placebo for a total of 3 injections at each dosing visit.

The dose of ustekinumab is weight dependent and will be administered at the dose recommended in the prescribing information.

TREATMENT- Rescue medication, emergency procedures, and additional treatments

There are no special emergency procedures to be followed.

Restricted medications were appropriate and are included below.

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 randomisation
brodalumab, ixekizumab	4 months prior to randomisation
adalimumab (Humira®) , infliximab (Remicade®) investigational products for psoriasis (non biologics)	12 weeks prior to randomisation
etanercept (Enbrel®) live virus vaccinations	6 weeks prior to randomisation
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 randomisation

Medication or class of medications	Restriction duration (through EOO Visit)
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 randomisation

[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.

- **Outcomes / endpoints**

Primary Endpoints

There are co-primary endpoints to assess the efficacy of risankizumabfor the treatment of moderate to severe chronic plaque psoriasis. These are as follows:

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

At the trial level, the co-primary endpoints will be the proportion of patients achieving PASI 90 and a sPGA score of clear or almost clear at week 16 in each of the treatment groups.

Secondary Endpoints

Key Secondary Endpoints:

The key secondary endpoints are as follows:

- Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 12
- Achievement of a sPGA score of clear or almost clear at Week 12
- Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16
- Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 52
- Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 52
- Change from baseline in psoriasis symptoms evaluated using the total score on the PSS at week 16
- Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16
- Achievement of total score on the PSS of 0 at week 16

Other Secondary Endpoints:

The secondary endpoints are as follows:

- Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 16
- Achievement of a sPGA score of clear or almost clear at Week 52
- Achievement of PASI 75 at Week 52

Further endpoints (summarised): included

- Various other PASI responses 50, 75, 90 and 100 at all visits collected
- Time to first achievement of PASI 50, 75, 90, 100, and sPGA 0 or 1
- Time to loss of PASI 75, 90, 100, and sPGA 0 or 1
- PSS total score of 0 at all visits collected
- Change from baseline in DLQI, HADS, HAQ-DI, swollen or tender joint count (28 joints) at all visits collected
- DAS (Disease Activity Score) 28 at all visits where HAQ-DI and swollen or tender joint count collected in patients selected for PsA assessment
- Change and percent change from baseline in Nail Psoriasis Severity Index (NAPSI) at all visits collected
- Change and percent change from baseline in Palmoplantar Psoriasis Severity Index (PPASI) at all visits collected
- Change and percent change from baseline in Psoriasis Scalp Severity Index (PSSI) at all visits collected
- Change of metabolic risk factors from baseline (waist circumference, body weight, HOMA-index)

Exploratory endpoints skin biopsy - biomarkers planned to be assessed by immunohistochemistry may include but not be limited to K16, Ki67 (on keratinocytes), S100 A7 (on keratinocytes), lipocalin-2 (NGAL), β-defensin 2, CD3+ T lymphocytes, CD11+ and DC lamp (Dendritic Cells).

- **Sample size**

Based on the outcome from the trials 1311.1 and 1311.2, the PASI 90 response rate at Week 16 is assumed to be at least 65% in the risankizumab arm and at most 45% in the ustekinumab arm.

The achievement of sPGA clear or almost clear rate at Week 16 is assumed to be at least 85% in the risankizumab arm and at most 67.5% in the ustekinumab arm.Using a 3:1 randomisation scheme (risankizumab:ustekinumab), 300 patients in the risankizumab arm and 100 in the ustekinumab arm will provide 94% power for PASI 90 AND will provide at least 95% power for the sPGA endpoint.

- **Randomisation**

An IRT will be used to allocate medication to patients through medication numbers.

Study drugs were administered subcutaneously. Injections were given in a double blind/dummy fashion with each patient receiving 2 injections of risankizumab or matching placebo and 1 injection of ustekinumab or matching placebo for a total of 3 injections at each dosing visit.

Randomisation was stratified by weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1).

- **Blinding (masking)**

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remain blinded with regard to the randomised treatment assignments until after database lock.

The randomisation code was kept confidential by Clinical Trial Support up to database lock.

Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded. Serum drug levels and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation and analysis in accordance with sponsor's standard procedures.

Unblinding and breaking the code

Emergency unblinding will be available to the investigator / pharmacist / investigational drug storage manager via IRT. It was only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding were to be documented in the source documents and/or appropriate eCRF page along with the date and the initials of the person who broke the code.

- **Statistical methods**

Statistical analyses of the primary and secondary efficacy endpoints were conducted in the Intention-to-treat population comprising all subjects randomised to one of the three treatment arms (risankizumab 150 mg, ustekinumab, and placebo) at week 0. Subjects were analysed according to the treatment group to which they were randomised, regardless of any protocol deviations.

The primary null hypothesis is that risankizumab is not different to placebo in achieving ≥ 90% reduction from baseline in the PASI score (PASI 90) and sPGA score of clear(0) or almost clear(1) at Week 16 in participants with moderate to severe chronic plaque psoriasis.

Testing of ranked secondary endpoints was conducted in a hierarchical manner, only if both co-primary endpoints were rejected.

The co-primary binary endpoints of PASI 90 and sPGA (0 or 1) were each analysed using the Cochran-Mantel Haenszel risk difference estimate stratified by the stratification factors of baseline weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1). The CMH weights proposed by Greenland and Robins were used.

Binary secondary endpoints were analysed using the same method as for the co-primary endpoints. Change from baseline in PSS at Week 16 was analysed using the stratified van Elteren test using the stratification factors of baseline weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1). Differences between treatment groups on other continuous variables were analysed using ANCOVA with treatment group, baseline value and stratification factors in the model.

Additional secondary analyses, without multiplicity control, included time-to-event analyses of time to first endpoint and time to loss of endpoint. Time-to-event data were analysed using Kaplan-Meier estimates for each treatment group and stratified log-rank tests for treatment group comparisons.

Consistency of the treatment effect for the primary efficacy endpoints was examined in subgroup analyses over demographic and other baseline characteristics including age, sex, race, smoking status, BMI, baseline PASI score, baseline sPGA, psoriatic arthritis status, past treatment history and region.

Similar analyses were conducted in the per-protocol population comprising subjects who were most compliant with the protocol in ways the sponsor believed could impact the observed treatment effect.

Last Observation Carried Forward was used as the primary method for handling missing values in continuous variables, and the secondary approach in the analyses of categorical variables.

Complete case (or as-observed case analysis) was used as the secondary method for handling missing values in continuous variables.

Multiple imputation was used as the sensitivity approach for the co-primary and ranked secondary endpoints. Imputation was primarily conducted under a missing at random assumption, although subjects who discontinued due to adverse event of “worsening of disease under study” were treated as non-responders at all subsequent visits.

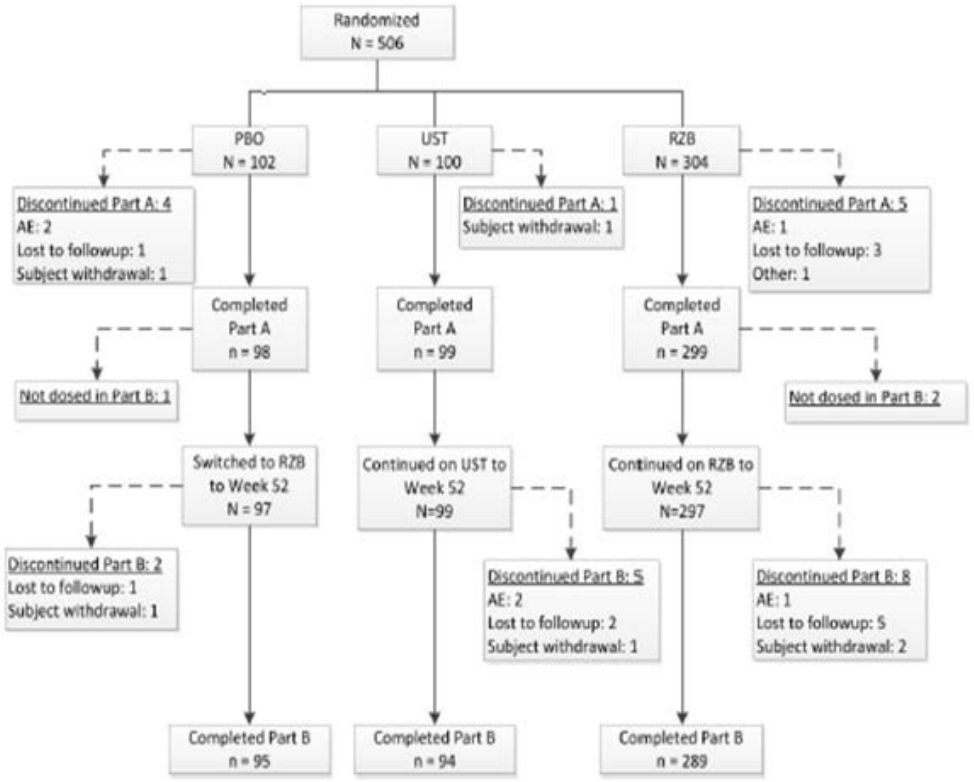
Logistic regression or MMRM models were proposed if multiple imputation approaches could not be applied to the collected data.

Results

- **Participant flow**

Study M16-008

A total of 506 subjects were randomized from 79 sites across 8 countries (Australia, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, and US). Similar proportions of subjects discontinued study drug prematurely in the placebo and risankizumab treatment groups through Week 16 of Part A.

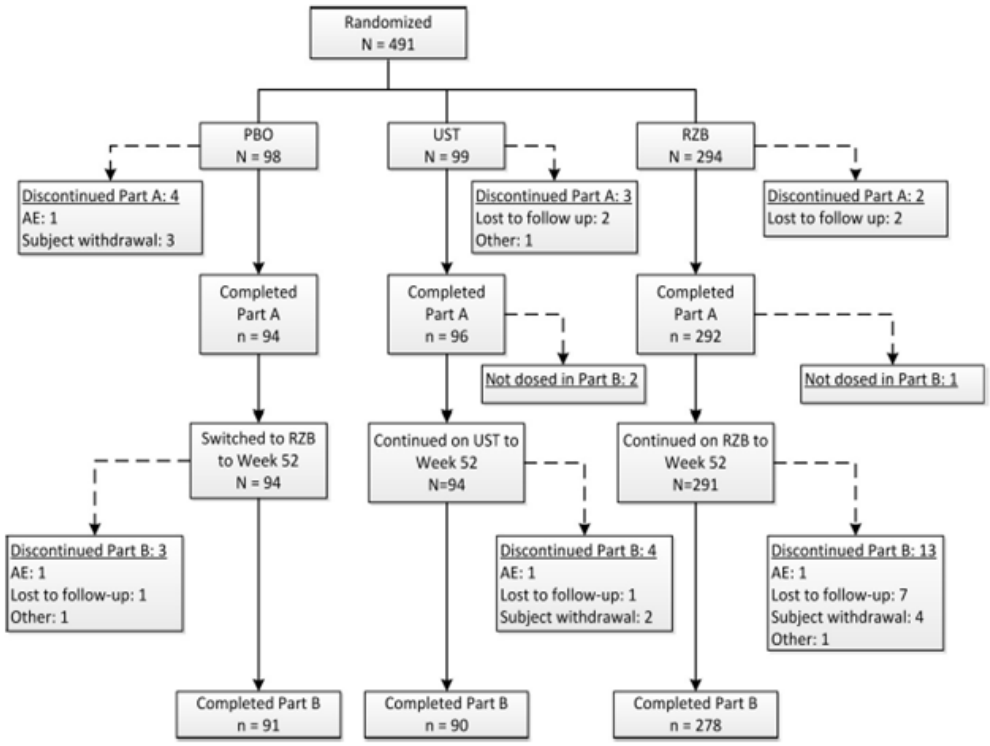


AE = adverse event; PBO = placebo; RZB = risankizumab; UST = ustekinumab

***Study* M15-995**

A total of 491 subjects were randomized from 64 sites across 10 countries (Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, and US). A larger proportion of subjects discontinued study drug prematurely in the placebo group compared to the risankizumab group through Week 16 of Part A.

For both studies through Week 52, the overall rate of premature discontinuation was low, and similar proportions of subjects on risankizumab or ustekinumab discontinued the study prematurely. Adverse events, lost to follow-up, and withdrawal by subject were the most frequently reported reasons for study drug discontinuation.



AE = adverse event; PBO = placebo; RZB = risankizumab; UST = ustekinumab

Protocol deviations:

Protocol deviations were defined in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines.

Table 4:Summary of Significant Protocol Deviations (ITT Population) M16-008

Protocol Deviation	PBO (N = 102) n (%)	UST (N = 100) n (%)	RZB (N = 304) n (%)	Total (N = 506) n (%)
Subjects who had at least 1 protocol deviation	0	0	10 (3.3)	10 (2.0)
Subject entered into the study even though she/he did not satisfy entry criteria	0	0	6 (2.0)	6 (1.2)
Subject who received wrong treatment or incorrect dose	0	0	1 (0.3)	1 (0.2)
Subject who received excluded or prohibited concomitant treatment	0	0	4 (1.3)	4 (0.8)
Subject who developed withdrawal criteria during the study and was not withdrawn	0	0	0	0

None of the deviations were considered to have affected the study outcome or interpretation of the study results or conclusions.

M15-995

Protocol deviation	PBO (N = 98) n (%)	UST (N = 99) n (%)	RZB (N = 294) n (%)	Total (N = 491) n (%)
Subjects who had at least 1 protocol deviation	2 (2.0)	2 (2.0)	11 (3.7)	15 (3.1)
Subject entered into the study even though she/he did not satisfy entry criteria	2 (2.0)	1 (1.0)	8 (2.7)	11 (2.2)
Subject who received wrong treatment or incorrect dose	0	1 (1.0)	0	1 (0.2)
Subject who received excluded or prohibited concomitant treatment	0	0	3 (1.0)	3 (0.6)
Subject who developed withdrawal criteria during the study and was not withdrawn	0	0	0	0

One Site was closed during study conduct due to failure of the site to adhere to the signed agreement, the study protocol and procedures, and GCP. The 11 subjects enrolled at this site were excluded from the efficacy and safety analyses as planned in the SAP.

A sensitivity analysis of the co-primary endpoints at Week 16 including these subjects was generated.

In addition to the deviations summarized above, a number of subjects had blood samples for evaluation of ADA and/or DNA banking drawn without signing a separate ICF that was required for these optional study procedures. In all instances, the subject was notified. If the subject did not agree to the sample being used for those purposes, the sample was destroyed. If the subject agreed to having the sample used, he/she was re-consented at the next visit. This was not considered to impact subject safety or subject rights.

- **Recruitment**

The protocol stated that the recruitment was competitive.

- **Conduct of the study**

The studies were conducted in accordance with the protocol, International Council for

Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki.

An Independent Ethics Committee/IRB approval of the protocol, informed consent, and subject information and/or advertising, as relevant, was obtained prior to the authorization of drug shipment to a study site.

Changes in conduct of the study

Both trials:

Substantive changes from the original protocol to Amendment 1 were to require an additional ADA sample was required at Week 4, to clarify the definition of analysis sets in the Statistical Methods upon a request from Health Authorities, and to add a definition for "time to onset of endpoint."

Substantive changes from Amendment 1 to Amendment 2 were to transition the US

Investigational New Drug application for risankizumab from BI to AbbVie, to change the sponsor for Study M16-008 within the US to AbbVie, and to change the Sponsor information and the ownership of various study responsibilities (e.g., statistical analysis).

None of the amendments are considered to have an impact on the integrity or interpretation of the data.

Statistical Changes

After the protocol was finalized, the rank order of the secondary endpoints was revised.

The company made 15 changes to the ranked secondary endpoints in both studies (see protocol), to be analyzed in the intent-to-treat (ITT) and per protocol (PP) Populations only if the null hypothesis for the co-primary endpoints has been rejected:

Other secondary endpoints included achievement of PASI 75 at Week 16, achievement of a sPGA of clear or almost clear at Week 52, and achievement of PASI 75 at Week 52.

Further efficacy endpoints were defined in statistical analysis plan (SAP). The SAP was finalized prior to blind break.

- **Baseline data**

The baseline demographics were similar between the treatment arms within each study. Comparing between the studies there were some differences M16-008 were slightly older but had a lower mean weight and lower mean BMI. There were more males than females in the study. The majority of patients were Caucasians.

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.

PASI, BSA, NAPSI, PSSI, PPASI, and PSS Scores at Baseline (ITT Population)

The baseline disease parameters are generally in line with entry criteria and were well-balanced between the study arms. 75% and 25% of study subjects were moderately and severely affected, respectively.

As psoriasis also affects nails scalp and plantar surfaces and also significantly impacts on patients quality of life the additional secondary efficacy endpoints examining the effect of treatment is agreed.

sPGA Scores at Baseline (ITT Population)

The applicant primarily targeted a moderate disease population average percent of moderate disease ranged 78.6 to 84.4%. The baseline disease severity s PGA was similar between treatment arms within the studies however comparing the studies M15-995 appears to have a higher percentage of more severe patients compared to study M16-008.However this is in line with other development programmes.

Disease History at Baseline (ITT Population)

Some differences were noted for each study that patients with psoriatic arthritis was higher for both placebo groups compared to both active arms. The applicant is asked to comment on whether this may have advantaged the Risankizumab treatment as patients with concomitant psoriatic arthritis may have more difficult disease to control.

Psoriasis Medication History (ITT Population)

The average amount of patients who had biologics ranged between 34.4 and 41.3 %, however a higher percentage of patients were treated with non-biologic systemic therapy 47.3- 51.6%. Approximately a third of patients were naïve to systemic therapy and 16.4 to 24.4 % of patients were naïve to all therapies (other than topical). Therefore the majority of patients were in the moderate category which is in line with s PGA data.

Exposure was comparable between treatment groups during Part A and Part B

Study Drug Exposure (Days) – All Randomized Subjects in Part A (ITT Population)

Study Drug Exposure (Days) – All Randomized Subjects in Part B (ITT Population).

The mean exposure was similar between treatment arms however study M16-008 had a slight longer cumulative duration of risankizumab.

- **Outcomes and estimation**

Primary Endpoints

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 5:Studies M15-995 (1311.28) and M16-008 (1311.3): Analysis Results of Primary Endpoints, NRI (ITT 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

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 Study M16-008).

The sensitivity analyses of the primary endpoints including the 11 subjects from one Site who were excluded from the efficacy analysis also yielded similar results (Study M15-995).

Ranked Secondary Endpoints

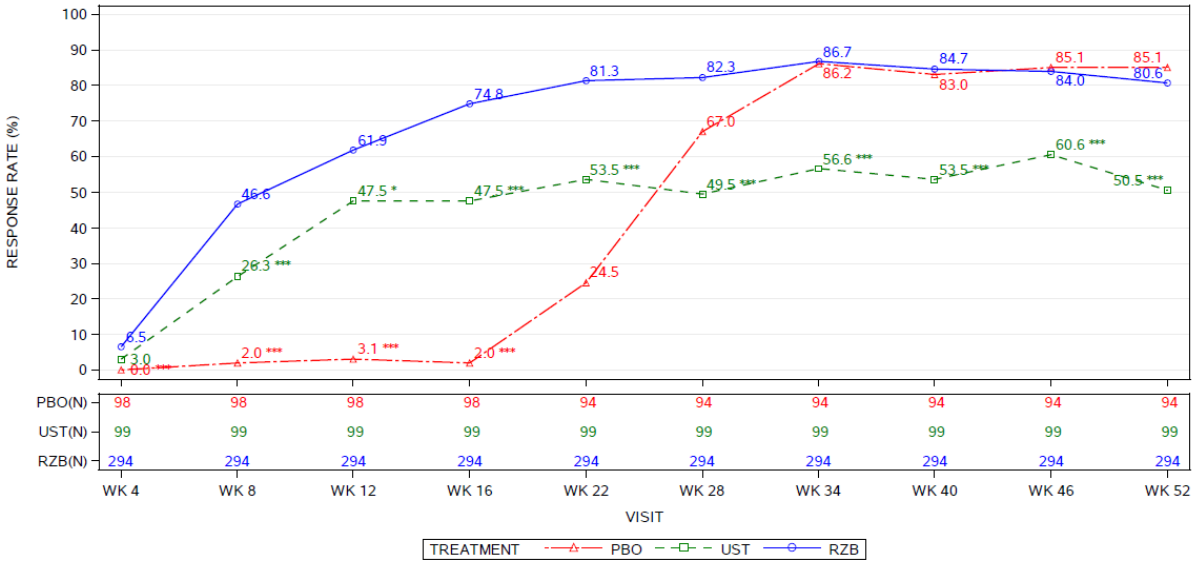
Risankizumab treatment was compared with placebo and ustekinumab treatment with respect to the ranked secondary endpoints PASI 100, PASI 90, PASI 75, sPGA clear, sPGA clear or almost clear, DLQI 0 or 1, and PSS at specified time points.

Statistically significant treatment effects favoring risankizumab were achieved for all ranked secondary endpoints in each study, indicating that risankizumab treatment was superior to placebo and ustekinumab.

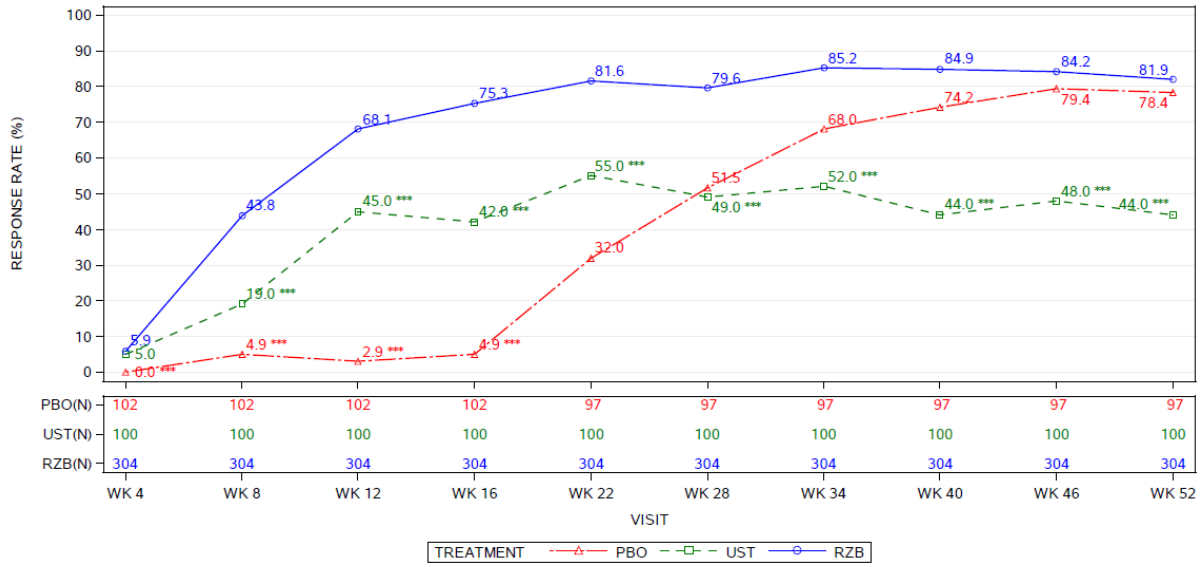
Table 6: Studies M15-995 (1311.28) and M16-008 (1311.3): Analysis Results of Ranked Secondary Endpoints (ITT Populations)

	Study					
	Study M15-995			Study M16-008		
	Risankizumab	Comparator		Risankizumab	Comparator	
Ranked Secondary Variable	n/N (%)	n/N (%)	*P*-value	n/N (%)	n/N (%)	*P*-value
1. sPGA clear at Week 16 (versus placebo)	150/294 (51.0)	3/98 (3.1)	< 0.001	112/304 (36.8)	2/102 (2.0)	< 0.001
2. PASI 100 at Week 16 (versus placebo)	149/294 (50.7)	2/98 (2.0)	< 0.001	109/304 (35.9)	0/102 (0)	< 0.001
3. DLQI 0/1 at Week 16 (versus placebo)	196/294 (66.7)	4/98 (4.1)	< 0.001	200/304 (65.8)	8/102 (7.8)	< 0.001
4. PSS of 0 at Week 16 (versus placebo)	92/294 (31.3)	0/98 (0)	< 0.001	89/304 (29.3)	2/102 (2.0)	< 0.001
5. PASI 90 at Week 16 (versus ustekinumab)	220/294 (74.8)	47/99 (47.5)	< 0.001	229/304 (75.3)	42/100 (42.0)	< 0.001
6. sPGA clear or almost clear at Week 16 (versus ustekinumab)	246/294 (83.7)	61/99 (61.6)	< 0.001	267/304 (87.8)	63/100 (63.0)	< 0.001
7. PASI 100 at Week 16 (versus ustekinumab)	149/294 (50.7)	24/99 (24.2)	< 0.001	109/304 (35.9)	12/100 (12.0)	< 0.001
8. sPGA clear at Week 16 (versus ustekinumab)	150/294 (51.0)	25/99 (25.3)	< 0.001	112/304 (36.8)	14/100 (14.0)	< 0.001
9. PASI 90 at Week 52 (versus ustekinumab)	237/294 (80.6)	50/99 (50.5)	< 0.001	249/304 (81.9)	44/100 (44.0)	< 0.001
10. PASI 100 at Week 52 (versus ustekinumab)	175/294 (59.5)	30/99 (30.3)	< 0.001	171/304 (56.3)	21/100 (21.0)	< 0.001
11. sPGA clear at Week 52 (versus ustekinumab)	175/294 (59.5)	30/99 (30.3)	< 0.001	175/304 (57.6)	21/100 (21.0)	< 0.001
12. PASI 75 at Week 12 (versus ustekinumab)	261/294 (88.8)	69/99 (69.7)	< 0.001	264/304 (86.8)	70/100 (70.0)	< 0.001
13. sPGA clear or almost clear at Week 12 (versus ustekinumab)	242/294 (82.3)	64/99 (64.6)	< 0.001	250/304 (82.2)	65/100 (65.0)	< 0.001
14. DLQI 0/1 at Week 16 (versus ustekinumab)	196/294 (66.7)	46/99 (46.5)	< 0.001	200/304 (65.8)	43/100 (43.0)	< 0.001
15. PSS total score (change from BL) at Week 16 (versus placebo)						
Within group LS mean change from BL (SE)	–6.402 (0.2193)	–0.027 (0.3316)	< 0.001	–5.608 (0.2254)	0.157 (0.3476)	< 0.001
Between group LS mean (95% CI)		–6.375 (–7.102, –5.648)			–5.765 (–6.496, –5.0350)	

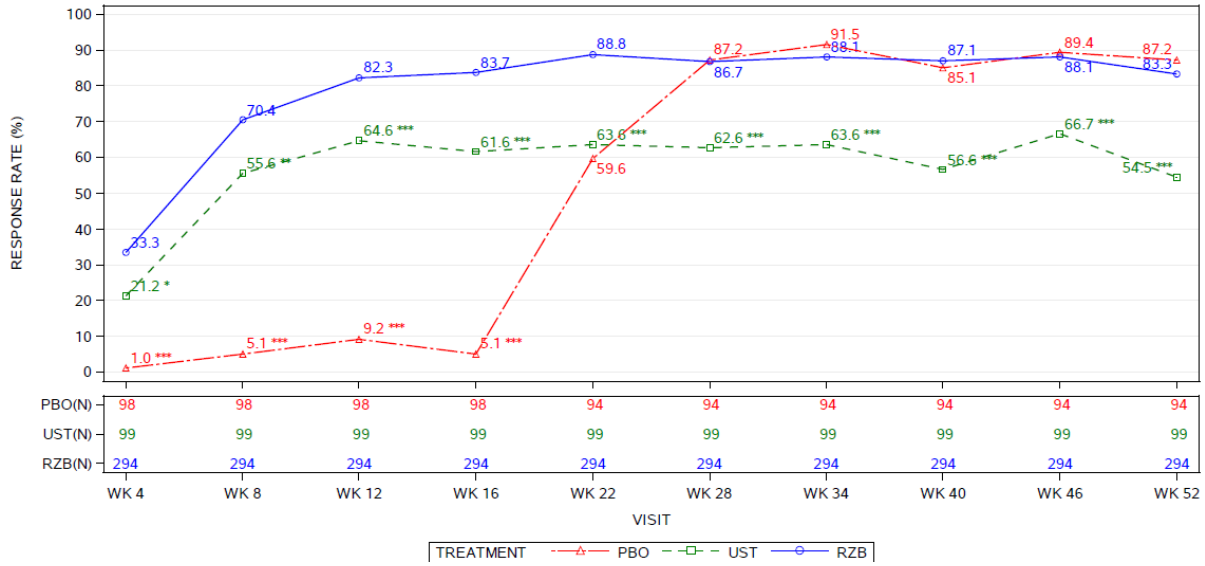
Response rate over time PASI 90 (study M15-995)



Response rate over time PASI 90 (study M16-008)



Response rates overtime s PGA clear or almost clear (study M15-995)



Response rates overtime s PGA clear or almost clear (study M16-008)

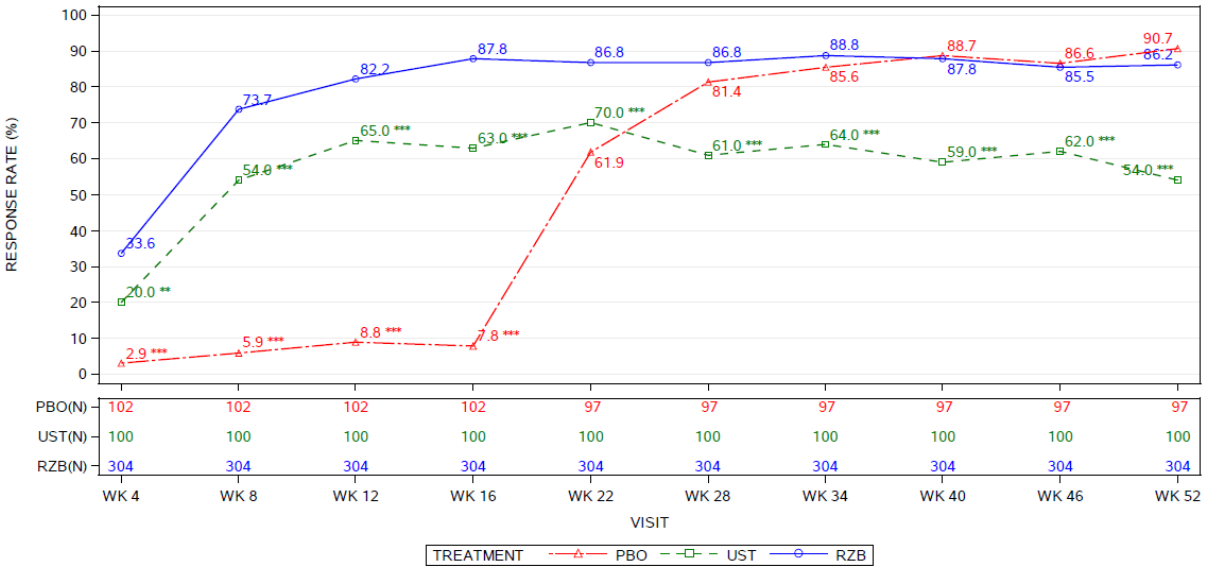


Table 7: Co-Primary Endpoints: PASI 90 and sPGA Clear or Almost Clear at Week 16, NRI (ITT Population) M16-008.

Assessment			Yes		No		Missing			Adjusted			Breslow-Day
Part	Treatment	N	n	%	n	%	n	%	Diff %	Diff %	95% CI[a]	*P* value[b]	*P*-value
PASI 90													
Part A	PBO	102	5	(4.9)	93	(91.2)	4	(3.9)	70.4	70.3	(64.0, 76.7)	< 0.001	0.474
	RZB	304	229	(75.3)	66	(21.7)	9	(3.0)					
sPGA clear or almost clear													
Part A	PBO	102	8	(7.8)	90	(88.2)	4	(3.9)	80.0	79.9	(73.5, 86.3)	< 0.001	0.953
	RZB	304	267	(87.8)	30	(9.9)	7	(2.3)					

CI = confidence interval; Diff = difference; ITT = intent-to-treat; NRI = non responder imputation; PBO = placebo; PASI = Psoriasis Area and Severity Index; PASI 90 = achievement of ≥ 90% reduction from baseline PASI score; sPGA = Static Physician Global Assessment; RZB = risankizumab; UST = ustekinumab

a. For Part A, CI and *P* values are computed for comparison between RZB versus UST, and RZB versus PBO. 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. If there was a stratum containing zero count, 0.1 was added to each cell. 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. If there was a stratum containing zero count, 0.1 was added to each cell. Within each stratum, *P* value was calculated based on chi-square test (or Fisher's exact test if ≥ 25% of the cells have expected cell count < 5).

Study M15-995

Assessment Part	Treatment	N	Yes n	Yes %	No n	No %	Missing n	Missing %	Diff %	Adjusted Diff %	95% CI[a]	P-value[b]	Breslow-Day P value
PASI 90													
Part A	PBO	98	2	(2.0)	92	(93.9)	4	(4.1)	72.8	72.5	(66.8, 78.2)	< 0.001	0.489
	RZB	294	220	(74.8)	71	(24.1)	3	(1.0)					
SPGA clear or almost clear													
Part A	PBO	98	5	(5.1)	89	(90.8)	4	(4.1)	78.6	78.5	(72.4, 84.5)	< 0.001	0.681
	RZB	294	246	(83.7)	45	(15.3)	3	(1.0)					

CI = confidence interval; Diff = difference; ITT = intent-to-treat; NRI = non responder imputation; PBO = placebo; PASI = Psoriasis Area and Severity Index; PASI 90 = achievement of ≥ 90% reduction from baseline PASI score; sPGA = Static Physician Global Assessment; RZB = risankizumab; UST = ustekinumab

a. For Part A, CI and *P* values are computed for comparison between RZB versus UST, and RZB versus PBO. 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. If there was a stratum containing zero count, 0.1 was added to each cell. 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. If there was a stratum containing zero count, 0.1 was added to each cell. Within each stratum, *P* value was calculated based on chi-square test (or Fisher's exact test if ≥ 25% of the cells have expected cell count < 5).

Statistically significant differences in favour of risankizumab versus placebo and ustekinumab were observed for the other secondary endpoints.

Study M15-995

Other Secondary Endpoints	Risankizumab n/N (%)	Comparator n/N (%)	Adjusted % Diff	*P* value
Proportion of subjects who achieved PASI 75 at Week 16 (versus placebo)	267/294 (90.8)	6/98 (6.1)	84.7	< 0.001
Proportion of subjects with sPGA score of clear or almost clear at Week 52 (versus ustekinumab)	245/294 (83.3)	54/99 (54.5)	29.1	< 0.001
Proportion of subjects who achieved PASI 75 at Week 52 (versus ustekinumab)	269/294 (91.5)	76/99 (76.8)	14.7	0.001

Study M16-008

Other Secondary Endpoints	Risankizumab n/N (%)	Comparator n/N (%)	Adjusted %Diff	*P* value
Proportion of subjects who achieved PASI 75 at Week 16 (versus placebo)	271/304 (89.1)	9/102 (8.8)	80.2	< 0.001
Proportion of subjects with sPGA score of clear or almost clear at Week 52 (versus ustekinumab)	262/304 (86.2)	54/100 (54.0)	32.4	< 0.001
Proportion of subjects who achieved PASI 75 at Week 52 (versus ustekinumab)	279/304 (91.8)	70/100 (70.0)	22.0	< 0.001

Starting at Week 12, statistically significant differences in favour of risankizumab for proportions of subjects who achieved all PASI 75/90/100, 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 randomized 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.

Other efficacy endpoints

Statistically significantly differences were observed between risankizumab and placebo groups at Week 16 on measures of improvement of nail psoriasis, palmoplantar psoriasis, and scalp psoriasis.

Improvement from baseline was also significantly better with risankizumab compared with ustekinumab for nail and scalp psoriasis at Week 52.

Quality of life endpoints

CHANGE FROM BASELINE IN DLQI (LOCF) BY VISIT (ITT POPULATION) study M16-008

PART VISIT	STRATA	TREATMENT	N	BASELINE MEAN	VISIT MEAN	WITHIN GROUP -CHANGE FROM BASELINE- LSMEAN	SE	BETWEEN GROUP COMPARISON -COMPARED TO RZB- LSMEAN DIFF	95% CI	SE	P-VALUE[A]
PART A WEEK 16											
	ALL										
		PBO	98	12.4	10.8	-1.9	0.45	-9.0	(-10.0, -8.0)	0.49	<0.001***
		UST	98	13.7	3.7	-9.2	0.46	-1.6	(-2.6, -0.6)	0.49	0.001**
		RZB	297	12.9	1.9	-10.8	0.29				
PART B WEEK 52											
	ALL										
		PBO/RZB	90	12.3	1.7	-11.1	0.39				
		UST/UST	98	13.7	3.9	-9.0	0.38	-2.5	(-3.3, -1.7)	0.40	<0.001***
		RZB/RZB	297	12.9	1.3	-11.5	0.24				

FOR COMPARISONS: ***, **, * STATISTICALLY SIGNIFICANT AT THE 0.001, 0.01, 0.05 LEVEL, RESPECTIVELY.

CHANGE FROM BASELINE IN DLQI (LOCF) BY VISIT (ITT POPULATION) study M15-995

PART VISIT	STRATA	TREATMENT	N	BASELINE MEAN	VISIT MEAN	WITHIN GROUP -CHANGE FROM BASELINE- LSMEAN	SE	BETWEEN GROUP COMPARISON -COMPARED TO RZB- LSMEAN DIFF	95% CI	SE	P-VALUE[A]
PART A WEEK 16											
	ALL										
		PBO	94	12.9	10.4	-2.6	0.43	-8.7	(-9.7, -7.8)	0.48	<0.001***
		UST	95	11.8	3.5	-9.3	0.44	-2.1	(-3.1, -1.2)	0.48	<0.001***
		RZB	290	13.6	1.9	-11.4	0.28				
PART B WEEK 52											
	ALL										
		PBO/RZB	82	12.8	1.4	-11.6	0.39				
		UST/UST	95	11.8	2.9	-10.0	0.37	-1.7	(-2.5, -0.9)	0.40	<0.001***
		RZB/RZB	290	13.6	1.4	-11.7	0.23				

FOR COMPARISONS: ***, **, * STATISTICALLY SIGNIFICANT AT THE 0.001, 0.01, 0.05 LEVEL, RESPECTIVELY.

2.5.2.2. Study: M16-010 (1311.30)

Study title (M16-010)-IMMvent

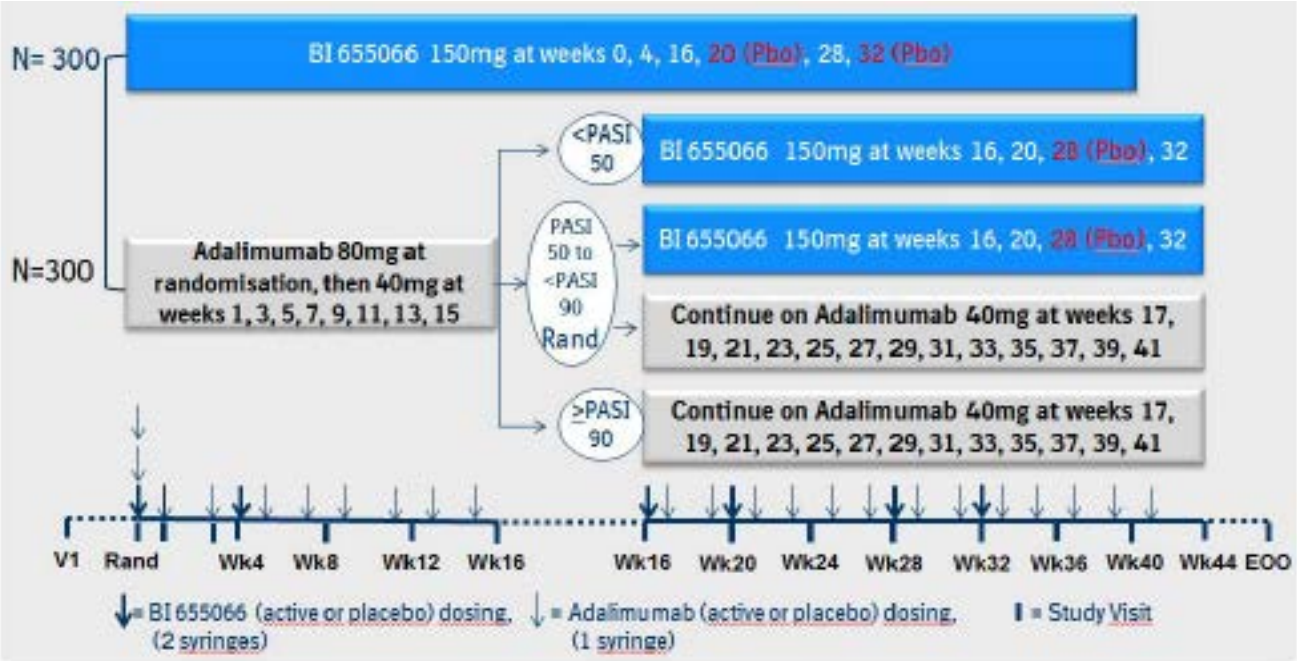
BI 655066/ABBV-066 (risankizumab) Versus Adalimumab in a Randomized, Double Blind, Parallel Group Trial in Moderate to Severe Plaque Psoriasis to Assess Safety and Efficacy After 16 Weeks of Treatment and After Incomplete Adalimumab Treatment Response (IMMvent).

- **Methods/ Study design**

This Phase 3, multi-national, multicentre, randomized, double-blind, double-dummy, active controlled, parallel-design study compared risankizumab(BI 655066) with adalimumab.

This study is designed to show a benefit of risankizumab over adalimumab in terms of PASI 90 response and sPGA scores of clear or almost clear at Week 16.

Study Design Schematic



Patients initially randomized to risankizumab will stay on risankizumab.

At Week 16, patients initially on adalimumab and <PASI 50 will be switched to risankizumab.

At Week 16, patients initially on adalimumab and >PASI 90 will stay on adalimumab.

At Week 16, patients initially on adalimumab and >PASI 50 and <PASI 90 will be re-randomised 1:1 to receive either risankizumab or adalimumab.

- **Study participants**

Inclusion criteria

- Adult men or women (at least 18 years of age)
- diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study agent
- stable moderate to severe chronic plaque psoriasis PASI ≥12, IGA ≥3, and involved BSA ≥10% at screening and at baseline
- Must be a candidate for phototherapy or systemic treatment for psoriasis
- Must be candidates for treatment with adalimumab (Humira®) according to local label as confirmed by the investigator

- Able and willing to self-administer the study medication
- Use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year

Exclusion criteria

- Non-plaque forms of psoriasis, drug-induced psoriasis, inflammatory diseases other than psoriasis that might confound trial evaluations
- Previous exposure to Risankizumab or Adalimumab
- Use of any restricted medication as specified
- Major surgery performed within 12 weeks
- Known chronic or relevant acute infections, such as active tuberculosis, HIV or viral hepatitis
- Any documented active or suspected malignancy or history of malignancy within 5 years

Patients were to be withdrawn if prohibited treatment is used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator. If the patient experiences an intolerable increase of psoriasis during the course of the trial.

- Treatments

Multiple doses of risankizumab, comparator drug adalimumab and matching placebos to both risankizumab and adalimumab were administered subcutaneously.

- Risankizumab was administered by 2 injections à 75mg at randomization, at Weeks 4, 16 and 28 for patients initially randomized to risankizumab and who continue on risankizumab; 2 injections 75mg at Weeks 16, 20 and 32 for patients crossing over from adalimumab to risankizumab at Week 16. The duration of treatment was therefore 16 or 28 weeks.

- Placebo Matching Risankizumab was given 0.9% sodium chloride solution presented in a pre-filled syringe. This was given as

a) 2 injections at Week 20 and 32 for patients who start with risankizumab and continue on risankizumab
b) 2 injections at randomization, Weeks 4 and 28 for patients switching from adalimumab to risankizumab at Week 16
c) 2 injections at randomization, Weeks 4, 16, 20, 28, and 32 for patients who start with adalimumab and continue on adalimumab.

-Adalimumab (Brand Name Humira) 2 injections à 40mg at randomization (80 mg loading dose), then 1 injection à 40mg at Weeks 1, 3, 5, 7, etc., every other week until Week 41 for patients who start with and continue on adalimumab; or only up to Week15 for patients who switch from adalimumab to Risankizumab at Week 16.

- Placebo to match Adalimumab. 0.9% sodium chloride solution presented in a pre-filled syringe. This was administered as 2 injections at randomization, followed by 1 injection at Weeks 1, 3, 5, 7 etc., every other week. Duration was 41 weeks in patients who started riszakizumab or 24 weeks for those who switched from Adalimumab to risankizumab.

Restrictions regarding concomitant treatment were the same as the same as the previous studies so are not mentioned again here.

- **Objectives**

The main objectives of this study are to assess the efficacy and safety of Risankizumab compared to adalimumab in patients with moderate to severe chronic plaque psoriasis. The primary efficacy evaluation will be performed at 16 weeks and an assessment of maintenance of response will be performed at 44 weeks. Evaluation of the efficacy of a 28 week treatment with Risankizumab in patients who had an insufficient or only partial response with adalimumab, and then switched to Risankizumab treatment from Week 16 to Week 44.

Assess PK and the emergence of anti-drug antibodies (ADA) and their effect on efficacy and safety. Influence on gene and protein expression levels and disease specific protein markers and metabolic risk factors

- **Outcomes/endpoints**

Primary Endpoint(s)

There are co-primary endpoints to assess the efficacy of risankizumab for the treatment of moderate to severe chronic plaque psoriasis. These are as follows:

Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16

Achievement of an sPGA score of clear or almost clear at Week 16.

Key Secondary Endpoints:

The key secondary endpoints are as follows:

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 ≥90% reduction from baseline PASI score (PASI 90) at Week 44 for those patients who are re-randomized at Week 16

Other Secondary Endpoints:

The other secondary endpoints are as follows:

Achievement of an sPGA score of clear or almost clear (0 or 1) at Week 44

Achievement of sPGA score of clear (0) at Week 44

Other endpoints

These were similar to the previous studies so are not presented in detail, here. Included PASI responses various levels, time to achieve PASI responses, s GPA, time to loss of response. Other efficacy endpoints NAPSI, PSSI, PPASI, DLQI

- **Randomisation**

After the eligibility criteria are confirmed, the patient will be randomized 1:1 to either risankizumab or adalimumab on Day 1 (Visit 2) through IRT call or website entry. At visits where study medication is to be administered or dispensed to the patient, study sites will be required to complete the medication resupply module in the Interactive Response Technology/Tool (IRT).

Randomization was stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1).

- **Blinding (masking)**

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial were to remain blinded with regard to the randomized treatment assignments until after database lock.

Emergency unblinding was available to the Investigator / Pharmacist / investigational drug storage manager via IRT in an emergency situations.

- **Statistical methods**

Part A

Statistical analyses of the co-primary and secondary efficacy endpoints were conducted in the Intention-to-treat population comprising all subjects randomised to one of the two treatment arms (risankizumab 150mg and adalimumab) at week 0. Subjects were analysed according to the treatment group to which they were randomised, regardless of any protocol deviations.

The primary null hypothesis is that risankizumab is not different to adalimumab in achieving ≥ 90% reduction from baseline in the PASI score (PASI 90) and sPGA score of clear (0) or almost clear(1) at Week 16 in participants with moderate to severe chronic plaque psoriasis.

In order to control the trial-wise type I error rate, both co-primary endpoints must be statistically significant simultaneously at the 5% level. Testing of ranked secondary endpoints was conducted in a hierarchical manner, only if both co-primary endpoints were rejected.

The co-primary binary endpoints of PASI 90 and sPGA (0 or 1) were each analysed using the Cochran-Mantel Haenszel risk difference estimate stratified by the stratification factors of baseline weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1). The CMH weights proposed by Greenland and Robins were used.

Binary secondary endpoints were analysed using the same method as for the co-primary endpoints. Differences between treatment groups on continuous variables were analysed using ANCOVA with treatment group, baseline value and stratification factors in the model.

Additional secondary analyses, without multiplicity control, included time-to-event analyses of time to first endpoint and time to loss of endpoint. Time-to-event outcome data were analysed using Kaplan-Meier estimates for each treatment group and stratified log-rank tests for treatment group comparisons.

Consistency of the treatment effect for the primary efficacy endpoints in Part A was examined in subgroup analyses over demographic and other baseline characteristics including age, sex, race, smoking status, BMI, baseline PASI score, baseline sPGA, psoriatic arthritis status, past treatment history and region.

Similar analyses were conducted in the per-protocol population comprising subjects who were most compliant with the protocol in ways the sponsor believed could impact the observed treatment effect.

The robustness of observed treatment effects for the co-primary and ranked secondary endpoints to alternative assumptions about the missing data mechanism was investigated in a number of sensitivity analyses.

Non-response imputation was the default method for handling missing data for the co-primary endpoints. All subjects who dropped out of the study were treated as non-responders in the primary efficacy analyses. Intermittent missing values were imputed as responders if the first non-missing values pre- and post- the missing visit both indicated response to treatment; otherwise they were imputed as non-response. Subjects that took prohibited medications to treat psoriasis were handled the same as those that discontinued from the trial – i.e. subsequent visits following start of prohibited medication were considered as failure for binary endpoints.

Last Observation Carried Forward was used as the primary method for handling missing values in continuous variables, and the secondary approach in the analyses of categorical variables.

Complete case (or as-observed case analysis) was used as the secondary method for handling missing values in continuous variables.

Multiple imputation was used as the sensitivity approach for the co-primary and ranked secondary endpoints. Imputation was primarily conducted under a missing at random assumption, although subjects who discontinued due to adverse event of "worsening of disease under study" were treated as non-responders at all subsequent visits.

Logistic regression or MMRM models were proposed should it not be possible to apply multiple imputation approaches to the collected data.

Part B

Statistical analyses of the primary and ranked secondary efficacy endpoint were conducted in the intention-to-treat population comprising all subjects re-randomised to one of the two treatment arms (risankizumab 150mg and adalimumab) at week 16. Subjects were analysed according to the treatment group to which they were randomised, regardless of any protocol deviations.

The primary null hypothesis is that risankizumab is not different to adalimumab in achieving ≥ 90% reduction from baseline in the PASI score (PASI 90) at Week 44 among patients re-randomized at Week 16. This endpoint will be tested independently with a type I error rate of 0.05

The null hypothesis for the single ranked secondary endpoint is that risankizumab is not different to adalimumab in the achievement of 100% reduction in baseline PASI score (PASI 100) at Week 44 among patients re-randomized at Week 16. This was tested using a two-sided test at the 5% level, only if the primary endpoint was rejected.

The primary binary endpoints of PASI 90 was analysed using the Cochran-Mantel Haenszel risk difference estimate stratified by the stratification factors of baseline weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1). The CMH weights proposed by Greenland and Robins were used.

Binary secondary endpoints were analysed using the same method as for the co-primary endpoints. Differences between treatment groups on other continuous variables were analysed using ANCOVA with treatment group, baseline value and stratification factors in the model.

Consistency of the treatment effect for the primary efficacy endpoints in Part B was examined in subgroup analyses over demographic and other baseline characteristics including age, sex, race, smoking status, BMI, baseline PASI score, baseline sPGA, psoriatic arthritis status, past treatment history and region.

Similar analyses were conducted in the per-protocol population comprising subjects who were most compliant with the protocol in ways the sponsor believed could impact the observed treatment effect.

Methods for handling missing data were identical to those for part A.

Efficacy Results

Participant flow

ADA = adalimumab; AE = adverse event; PASI = Psoriasis Area and Severity Index; RZB = risankizumab

- **Outcomes and estimation**

Primary endpoint result

The primary efficacy analyses were conducted in the ITT population in Part A (ITT_A) and the ITT re-randomized population in Part B (ITT_B_RR). Only the primary and ranked secondary variables were analyzed for the per-protocol populations using the methods of handling missing data described in the SAP.

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. Sensitivity and per protocol analyses supported the primary analysis. Point estimates were consistently in favour of the risankizumab group across strata.

Table 8: Proportion of Subjects in Adalimumab and Risankizumab Groups Who Achieved PASI 90 and sPGA Clear or Almost Clear at Week 16, NRI (ITT_A 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.

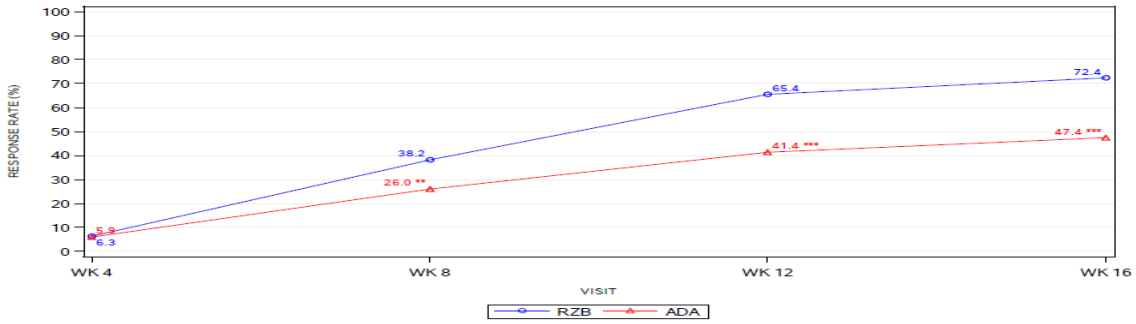
b. Across the strata, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

Note: For Part A, CI and *P* values were computed for comparison between risankizumab vs adalimumab.

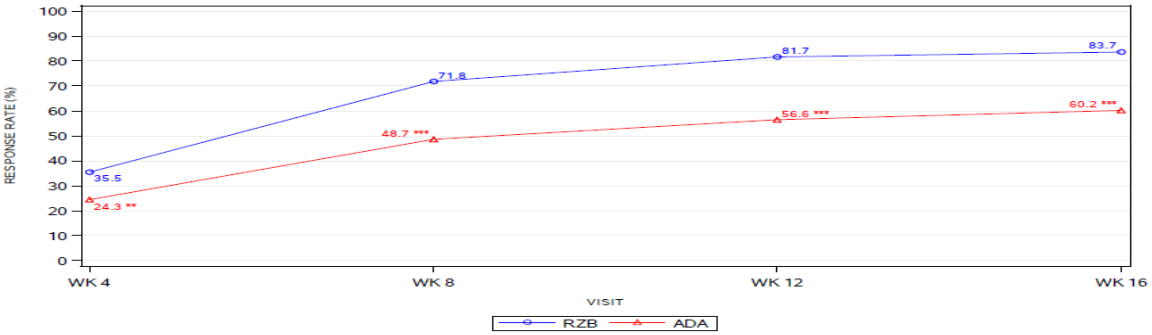
Subgroup analyses were in favour of risankizumab with 95% confidence intervals of the treatment difference excluding zero in the vast majority of the subgroups for PASI 90 and sPGA clear or almost clear. See additional analyses below.

Sensitivity analyses also supported the superiority of riszankizumab compared to Adalimumab.

Response rate over time in PASI 90 (Part A ITT population).



Response rate over time in s PGA 0 / 1 (Part A ITT population).



Primary Endpoint in Part B

At Week 16, patients initially on adalimumab and >PASI 50 and <PASI 90 were re-randomised 1:1 to receive either risankizumab or adalimumab.

The primary endpoint in Part B was achieved a statistically significantly larger proportion of subjects who were re-randomized to risankizumab achieved PASI 90 at Week 44 compared with subjects who were re-randomized to adalimumab.

Sensitivity and per protocol analyses supported the primary analysis.

Table 9: Proportion of Subjects Re-Randomized to Adalimumab and Risankizumab Who Achieved PASI 90 at Week 44, NRI (ITT_B_RR Population)

Treatment	N	Yes		No		Missing		Diff %	Adjusted Diff %	95% CI[a]	P-value[b]	Breslow-Day P-value
		n	%	n	%	n	%					
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.

In addition to the pre-specified subgroup analyses, the proportion of re-randomized subjects (PASI 50 to < PASI 90) who achieved PASI 90 at Week 44 was analyzed by subgroups based on PASI response at the entry to Part B: < PASI 75 and ≥ PASI 75. In each subgroup, a statistically significantly larger proportion of subjects who were re-randomized to risankizumab achieved PASI 90 at Week 44 compared with subjects who were re-randomized to adalimumab.

Pre-specified subgroup analyses also supported the data as in each subgroup, a statistically significantly improvement was demonstrated.

Table 10: Proportion of Re-Randomized Subjects Who Achieved PASI 90 at Week 44 by PASI Score Subgroup at Entry to Part B, NRI (ITT_B_RR Population)

Group	ADA/ADA n/N (%)	ADA/RZB n/N (%)	Adjusted 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

Ranked Secondary Efficacy Endpoints

Risankizumab was statistically significantly superior to adalimumab on all ranked secondary endpoints.

Table 11: Statistical Results for Ranked Secondary Endpoints in Part A Presented in Rank Order (ITT_A Population)

Ranked Secondary Variable	ADA n/N (%)	RZB n/N (%)	Adjusted Difference %	P value[a]
1. Proportion of subjects who achieved PASI 75 at Week 16	218/304 (71.7)	273/301 (90.7)	18.9	< 0.001
2. Proportion of subjects who achieved PASI 100 at Week 16	70/304 (23.0)	120/301 (39.9)	16.7	< 0.001

ADA = adalimumab; PASI = Psoriasis Area and Severity Index; RZB = risankizumab

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

Part B

Among subjects randomized to receive adalimumab who had inadequate response.

(PASI 50 to < PASI 90) at Week 16, a statistically significantly larger proportion of subjects who were re-randomized to risankizumab achieved PASI 100 at Week 44 compared with subjects who were re-randomized to adalimumab.

Table 12: Proportion of Re-Randomized Subjects Who Achieved PASI 100 at Week 44, NRI (ITT_B_RR Population)

ADA/ADA	ADA/RZB	Adjusted	
n/N (%)	n/N (%)	Difference %	*P* value[a]
4/56 (7.1)	21/53 (39.6)	32.8	< 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.

Further Efficacy Endpoints

Part A

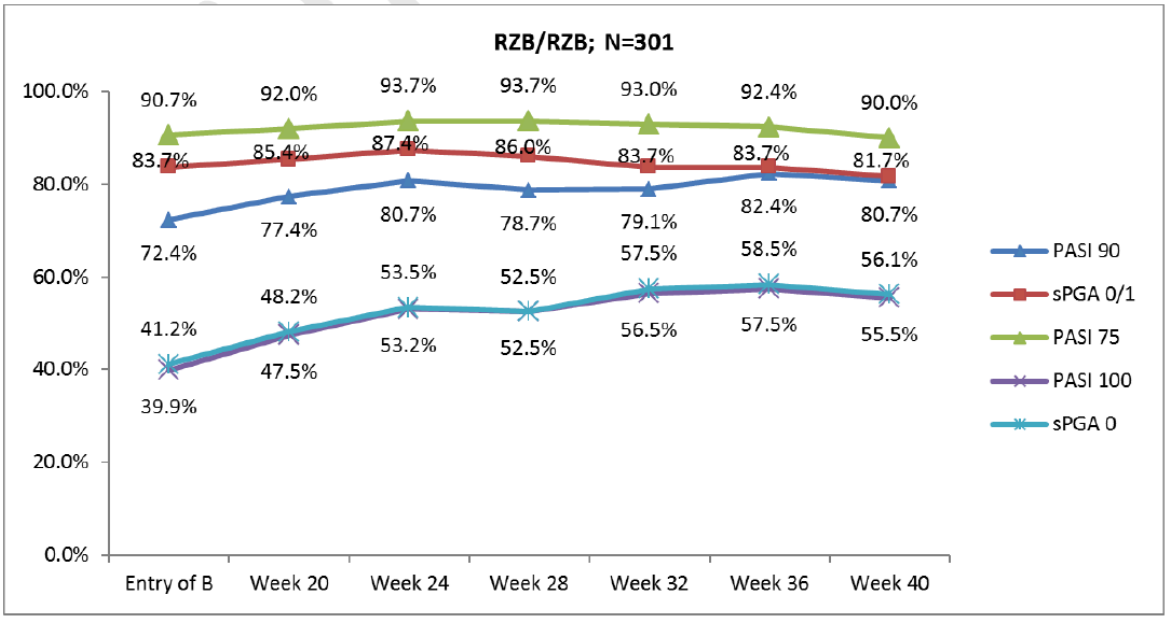
Proportion of Subjects Achieving PASI and sPGA Response Over Time (Part A)

Statistically significant differences in favour of risankizumab were observed between risankizumab and adalimumab groups on measures of improvement of palmoplantar psoriasis (PPASI -6.58 and -5.20 respectively; p=0.036) and scalp psoriasis (PSSI -19.5 and -17.7; p=<0.001) at Week 16. Both treatments showed improvement in nail psoriasis; however, the difference between treatment groups was not statistically significant (NAPSI -9.6 and -11.7; p=0.095) at Week 16.

Part B

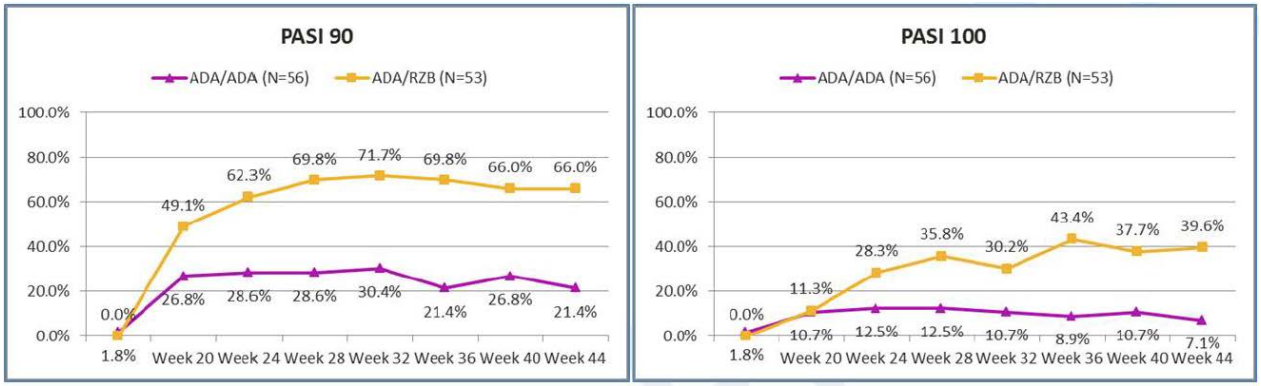
Subjects who received continuous risankizumab saw persistent or increased responses until the end of the study; 157/301 (52.2%) achieved sPGA clear and 159/301 (52.8%) achieved PASI 100 at Week 44.

Proportion of Subjects Achieving PASI and sPGA Response Over Time with Continuous RZB Treatment (Part B)



Subjects who were non-responders to adalimumab (< PASI 50 at Week 16) received clinical benefit from switching to risankizumab, with > 60% achieving PASI 90 and sPGA clear or almost clear at Week 44. At Week 44, statistically significantly (P < 0.001) higher proportion of subjects re-randomized to risankizumab achieved PASI 90 and PASI 100 response compared to those re-randomized to continue adalimumab. The statistical significance was observed as early Week 20 (for PASI 90) and Week 24 (PASI 100).

Proportion of Subjects Achieving PASI Response Over Time (Part B)



Quality of Life Results and Conclusions

A statistically significantly larger proportion of subjects in the risankizumab group (65.8%) achieved Dermatology Life Quality Index (DLQI) of 0 or 1 at Week 16 compared with the adalimumab group (48.7%).

Additional analyses (subgroup analyses week 16).

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

Table 13: Proportion of Subjects Who Achieved PASI 90 at Week 16 by Subgroup, NRI (ITT_A Population).

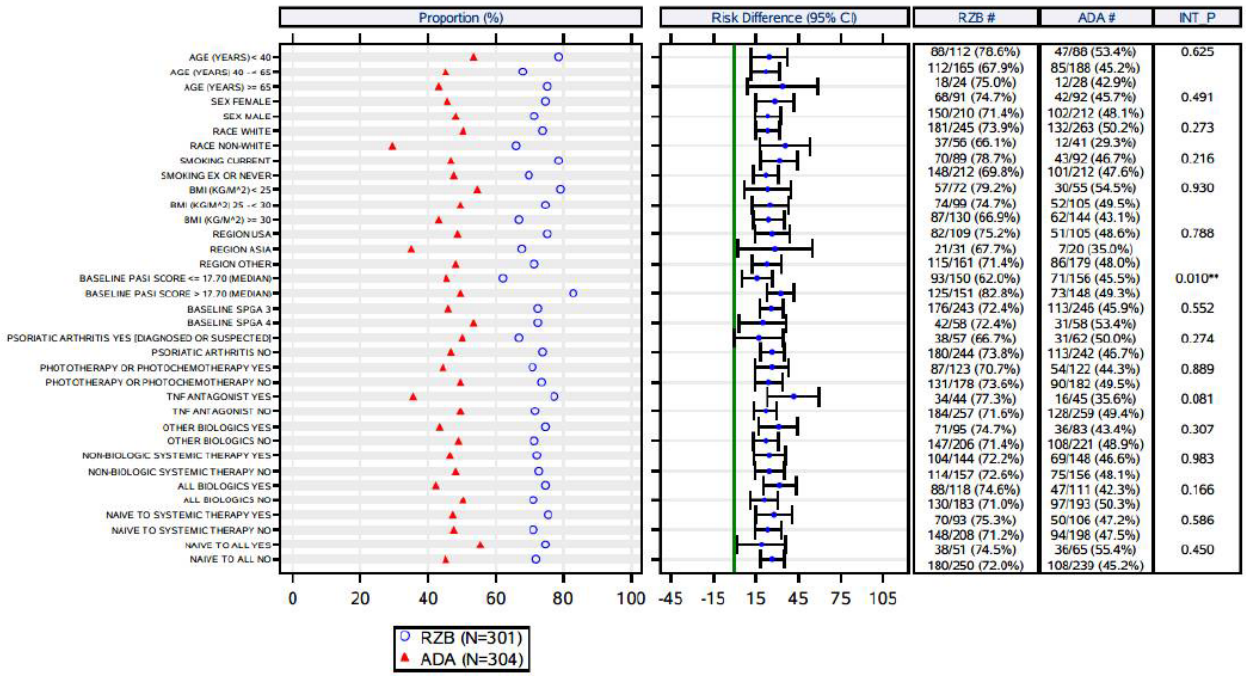
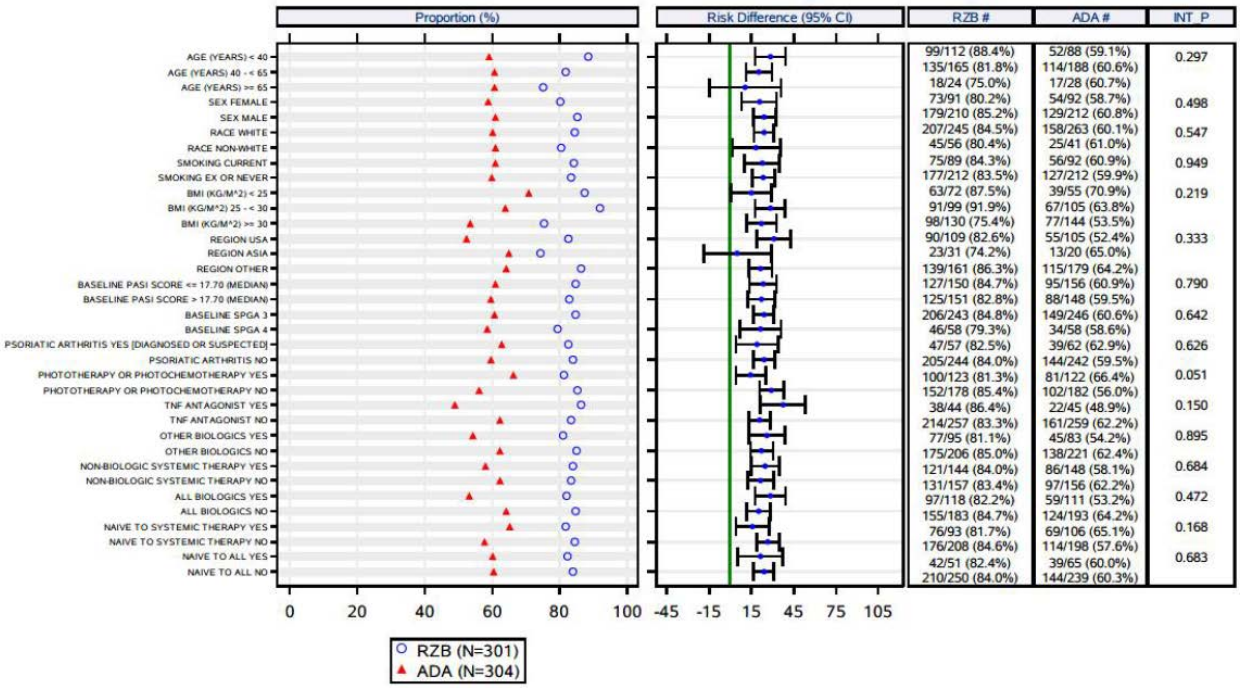


Table 14: Proportion of Subjects Who Achieved sPGA Clear or Almost Clear at Week 16 by Subgroup, NRI (ITT_A Population)



2.5.2.3. Study M15-992 (1311.4)

Title: BI 655066 [risankizumab] Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment

- **Methods**

This Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study compares risankizumab with placebo in the treatment of moderate to severe chronic plaque psoriasis. It includes 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.

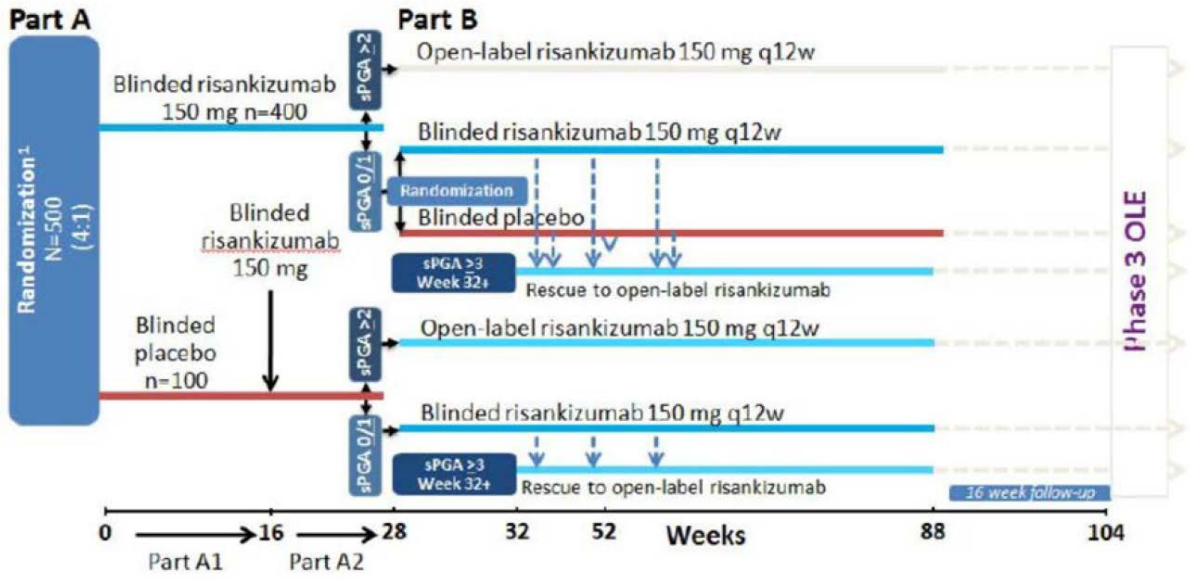
Eligible subjects were randomized at a ratio of 4:1 to one of 2 treatment arms.

At the Week 16 visit (co-primary endpoints), all subjects were to receive risankizumab 150 mg active treatment.

At the Week 28 visit, all subjects were to be assessed for response. Subjects in Arm 1 who met the protocol-defined response criterion (Static Physician Global Assessment [sPGA] clear or almost clear) were to be re-randomized in a ratio of 1:2 to double-blind risankizumab or placebo, while subjects who did not meet the criterion were to receive open-label risankizumab 150 mg from Week 28 through Week 88, while all subjects in Arm 2 who met the criterion were to receive blinded risankizumab 150 mg at Week 28. After the end of treatment (EOT) at Week 88, all subjects were to continue in the 16 week follow-up period. Beginning at Week 32, all subjects in both arms who received blinded study drug at Week 28 and had sPGA ≥ 3 (relapse) were to be switched to open-label risankizumab. If relapse occurred from Week 32 through Week 70, open-label risankizumab 150 mg was to be administered at 0, 4, and 16 weeks after relapse. If relapse occurred after Week 70 through Week 82, open-label risankizumab 150

mg was to be administered at 0 and 4 weeks after relapse. If relapse occurred after Week 82 through Week 88, the subject was to receive re-treatment with a single dose of risankizumab.

Figure 1: Trial design



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

- **Study participants**

Adult subjects were enrolled with moderate to severe plaque psoriasis, defined by a PASI≥12, sPGA ≥3, and BSA involvement of at least 10%, who were candidates for systemic or phototherapy. Enrolment criteria were well in accordance with the EMA psoriasis guideline requirements.

- **The main exclusion criteria**

Following patients were excluded:

Patients with non-plaque forms of psoriasis, current drug-induced psoriasis, active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to the investigator's judgment.

Patients who had known chronic or relevant acute infections, such as HIV (Human Immunodeficiency Virus), viral hepatitis, or tuberculosis, any documented active or suspected malignancy or history of malignancy within 5years prior to screening. Patients with latent tuberculosis with low risk of reactivation could be enrolled.

- **Treatments**

Risankizumab and matching placebo were to be administered in the study. Risankizumab 150 mg for subcutaneous (SC) administration was to be provided in 2 pre-filled syringes (PFS) of 75 mg each. Placebo was also to be administered subcutaneously via a PFS.

- **Objectives**

The primary objectives of this trial are to assess the safety and efficacy of risankizumab 150 mg in comparison to placebo in patients with moderate to severe chronic plaque psoriasis. The primary efficacy evaluation was performed at 16 weeks. In addition, the maintenance of response following drug withdrawal was assessed after Week 28 through Week 104.

Subsequent to drug withdrawal, patients who experience relapse were retreated with risankizumab to assess response after retreatment.

- **Outcomes/endpoints**

Primary Endpoints:

The co-primary efficacy endpoints in Part A1: Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16 and achievement of sPGA of clear or almost clear (0 or 1) at Week 16.

The primary efficacy endpoint in Part B: Achievement of sPGA clear or almost clear response at Week 52.

Key Secondary Endpoints:

Ranked secondary endpoints in Part A1

- 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
- Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16
- Ranked secondary endpoints in Part B: achievement of sPGA of clear or almost clear at Week 104. Of note, this endpoint will be analyzed in the final clinical study report (CSR).

Other Secondary Endpoints Further endpoints see clinical AR's.

- **Sample size**

Based on the interim results from 1311.2 (c03272682-01), it is assumed at most 10% of the patients in the re-randomized risankizumabarm will lose sPGA response of clear or almost clear (0 or 1) at Week 52 whereas approximately 25% of patients in the re-randomized placebo arm will lose response. Using a 4:1 randomisation will yield a total sample size of 500 = 400:100 for risankizumab: placebo. Based on the outcome from trials 1311.1 and 1311.2, the PASI 90 response rate at Week 16 is assumed to be at least 65% in the risankizumab arm and approximately 5% for placebo. For sPGA clear or almost clear at Week 16, the response rate for the risankizumab arm is assumed to be at least 80% and approximately 5% for placebo. This trial will have >99% power for comparing each risankizumab arm to placebo on both of these endpoints.

- **Randomisation**

At Visit 2, patients were randomized in blocks to double-blind treatment to either risankizumab 150 mg or placebo in a 4:1 ratio. Randomisation will be stratified with respect to weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1). At week 28, patients were separated into "responder" and "non-responder" groups. A patient were considered as a "responder" if the week 28 sPGA is clear or almost clear (0 or 1); otherwise the patient were considered a "non-responder". Among responders, patients originally randomized to risankizumab 150 mg (Arm 1) were rerandomized in a 1:2 ratio to either 150 mg of risankizumab or placebo in a second double-blinded portion (Part B) of the trial. Re-randomisation was stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1). Patients originally randomized to placebo (Arm 2) continued to receive blinded study drug every 12 weeks in Part B of the trial, to maintain the blind to the original randomized treatment arm.

Regardless of originally randomized treatment group, non-responders received open label risankizumab every 12 weeks, starting at Week 28, for the remainder of the trial.

- **Blinding (masking)**

During "Part A" of this trial all patients received double-blind treatment. At Week 28, the start of "Part B", non-responders (sPGA≥ 2) from Arm 1 and 2 received open label drug and will know future treatments are risankizumab.

At Week 28, responders (sPGA of 0 or 1) from Arm 1 in "Part A" were re-randomized to either maintain treatment of risankizumab or to receive placebo; these treatments were be double-blinded to ensure that patients and investigators remain blinded to re-randomized treatment during "Part B." To maintain blinding, if a patient in Arm 2 reaches a sPGA of 0 or 1 at Week 28, continued to receive blinded risankizumab treatment assigned from IRT.

- **Statistical methods**

Part A

Statistical analyses of the primary and secondary efficacy endpoints were conducted in the Intention-to-treat population comprising all subjects randomised to one of the two treatment arms (risankizumab 150 mg and placebo) at week 0. Subjects were analysed according to the treatment group to which they were randomised, regardless of any protocol deviations.

The primary null hypothesis is that risankizumab is not different to placebo in achieving ≥ 90% reduction from baseline in the PASI score (PASI 90) and sPGA score of clear(0) or almost clear (1) at week 16 in participants with moderate to severe chronic plaque psoriasis.

In order to control the trial-wise type I error rate, both co-primary endpoints must be statistically significant simultaneously at the 5% level. Testing of ranked secondary endpoints was conducted in a hierarchical manner, only if both co-primary endpoints were rejected.

The co-primary binary endpoints of PASI and sPGA (0 or 1) were each analysed using the Cochran-Mantel Haenszel risk difference estimate stratified by the stratification factors of baseline weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1). The CMH weights proposed by Greenland and Robins were used.

Binary secondary endpoints were analysed using the same method as for the co-primary endpoints. Differences between treatment groups on other continuous variables were analysed using ANCOVA with treatment group, baseline value and stratification factors in the model.

Additional secondary analyses, without multiplicity control, included time-to-event analyses of time to first endpoint and time to loss of endpoint, analysed using Kaplan-Meier estimates for each treatment group and stratified log-rank tests for treatment group comparisons.

Consistency of the treatment effect for the primary efficacy endpoints was examined in subgroup analyses over demographic and other baseline characteristics including age, sex, race, smoking status, BMI, baseline PASI score, baseline sPGA, psoriatic arthritis status, past treatment history and region.

Similar analyses were conducted in the per-protocol population comprising subjects who were most compliant with the protocol in ways the sponsor believed could impact the observed treatment effect.

The robustness of observed treatment effects for the co-primary and ranked secondary endpoints to alternative assumptions about the missing data mechanism was investigated in a number of sensitivity analyses.

Non-response imputation was the default method for handling missing data for the co-primary endpoints. All subjects who dropped out of the study were treated as non-responders in the primary efficacy analyses. Intermittent missing values were imputed as responders if the first non-missing values pre- and post- the missing visit both indicated response to treatment; otherwise they were imputed as non-response. Subjects that took prohibited medications to treat psoriasis were handled the same as those that discontinued from the trial – i.e. subsequent visits following start of prohibited medication were considered as failure for binary endpoints.

Last Observation Carried Forward was used as the primary method for handling missing values in continuous variables, and the secondary approach in the analyses of categorical variables.

Complete case (or as-observed case analysis) was used as the secondary method for handling missing values in continuous variables.

Multiple imputation was used as the sensitivity approach for the co-primary and ranked secondary endpoints. Imputation was primarily conducted under a missing at random assumption, although subjects who discontinued due to adverse event of “worsening of disease under study” were treated as non-responders at all subsequent visits.

Logistic regression or MMRM models were proposed should it not be possible to apply multiple imputation approaches to the collected data.

Part B

Statistical analyses of the primary and ranked secondary efficacy endpoint were conducted in the intention-to-treat population comprising all subjects who were initially randomized to risankizumab 150 mg and were subsequently re-randomised to one of the two treatment arms (risankizumab 150mg or placebo) at week 28. Subjects were analysed according to the treatment group to which they were randomised, regardless of any protocol deviations.

The primary null hypothesis is that risankizumab is not different to placebo in achieving sPGA score of clear(0) or almost clear(1) at Week 52 among patients re-randomized at Week 28. This endpoint will be tested independently with a type I error rate of 0.05

The null hypothesis for the single ranked secondary endpoint is that risankizumab is not different to placebo in the achievement of sPGA score of clear (0) or almost clear (1) at Week 52 among patients re-randomized at Week 28. This was tested using a two-sided test at the 5% level, only if the primary endpoint was rejected.

The primary binary endpoint of sPGA (0 or 1) was analysed using the Cochran-Mantel Haenszel risk difference estimate stratified by the stratification factors of baseline weight (≤ 100 kg versus >100 kg)

and prior exposure to TNF antagonists (0 versus ≥1). The CMH weights proposed by Greenland and Robins were used.

Binary secondary endpoints were analysed using the same method as for the co-primary endpoints. Differences between treatment groups on other continuous variables were analysed using ANCOVA with treatment group, baseline value and stratification factors in the model.

Time to loss of response and time to relapse were performed among those achieving response at-re-randomization, analysed using Kaplan-Meier estimates for each treatment group and stratified log-rank tests for treatment group comparisons.

Consistency of the treatment effect for the primary efficacy endpoints in Part B was examined in subgroup analyses over demographic and other baseline characteristics including age, sex, race, smoking status, BMI, baseline PASI score, baseline sPGA, psoriatic arthritis status, past treatment history and region.

Similar analyses were conducted in the per-protocol population comprising subjects who were most compliant with the protocol in ways the sponsor believed could impact the observed treatment effect.

Methods for handling missing data were identical to those for part A.

Results

- **Participant flow**

A total of 507 subjects were randomized from 60 sites across 9 countries. Similar proportions of subjects discontinued study drug prematurely in the placebo and risankizumab treatment groups through Week 16 (Part A1). Through Week 28, subjects who were randomized to risankizumab and received study drug at Weeks 0, 4, and 16 had low rates of premature discontinuation. Of the 407 subjects randomized to risankizumab, 403 completed Part A1 (through Week 16) and 399 completed Part A2 (through Week 28) and continued to Part B; 336 were sPGA clear or almost clear responders at Week 28. These responders were re-randomized in a ratio of 2:1 to withdrawal from risankizumab treatment (placebo;n = 225) or continue risankizumab treatment (n = 111) in Part B. Similar proportions of subjects discontinued from the study prematurely in re-randomized treatment groups (see figures below).

Figure 2: Subject Disposition, Part A

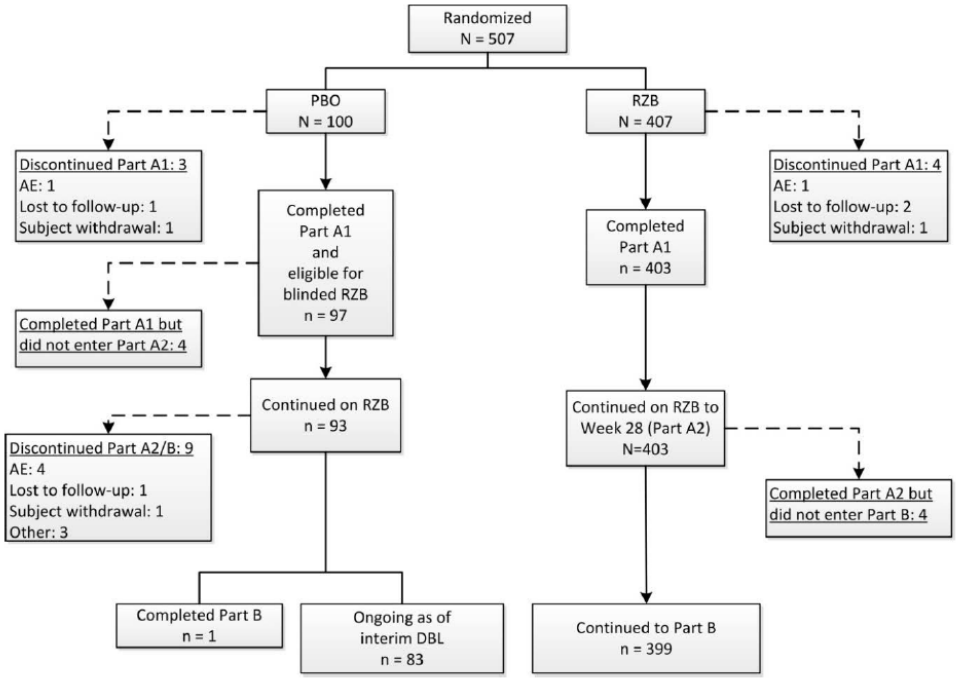
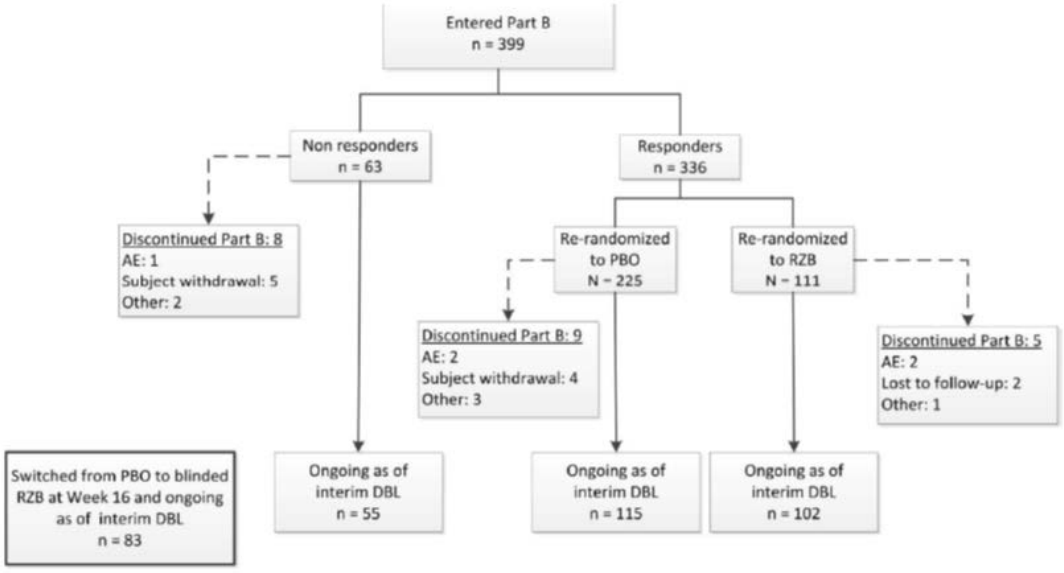


Figure 3: Subject Disposition, Part A1 RZB-Treated Subjects that Entered Part B



AE = adverse event; DBL = database lock; PBO = placebo; RZB = risankizumab

- **Conduct of the study**

Changes in the Conduct of the Study or Planned Analyses

- Amendments

The original protocol (22 October 2015, 127 subjects) had 3 protocol amendments and 1 announcement of change.

During the amendment 2 the trial design was amended to protect the blind to initial randomized treatment. In the amended protocol, all subjects who had sPGA < 2 at Week 28 continued to receive blinded study drug, regardless of initial treatment group. Likewise, subjects who had sPGA ≥ 2 at Week 28 received open-label risankizumab at Week 28 and every 12 weeks (q12w) thereafter, regardless of initial treatment group. This amendment was put in place before any subject reached the Week 28 visit.

- Statistical Changes

There were no changes in the analyses after finalization of the SAP.

- Protocol Deviations

Small number of protocol deviations were reported in this interim analysis.

Table 15: Summary of Significant Protocol Deviations

Protocol Deviation	PBO (N = 100) n (%)	RZB (N = 407) n (%)	Total (N = 507) n (%)
Subjects who had at least 1 protocol deviation	3 (3.0)	18 (4.4)	21 (4.1)
Subject entered into the study even though she/he did not satisfy entry criteria	2 (2.0)	8 (2.0)	10 (2.0)
Subject who received wrong treatment or incorrect dose	0	5 (1.2)	5 (1.0)
Subject who received excluded or prohibited concomitant treatment	1 (1.0)	5 (1.2)	6 (1.2)
Subject who developed withdrawal criteria during the study and was not withdrawn	0	0	0

PBO = subjects randomized to placebo in Part A; RZB = subjects randomized to risankizumab in Part A

- **Baseline data**

Demographic Characteristics

Part A1 (from the beginning of the study to week 16 which the time for the primary endpoint assessment)

Two groups:

- RZB: Subjects who were randomized to risankizumab 150 mg
- PBO: Subjects who were randomized to placebo

Table 16: Demographic Characteristics of All Randomized Subjects, Categorical Variables (ITT_A1 Population)

Variable	PBO (N = 100) n (%)	RZB (N = 407) n (%)	Total (N = 507) n (%)
Sex			
Female	27 (27.0)	124 (30.5)	151 (29.8)
Male	73 (73.0)	283 (69.5)	356 (70.2)
Age (years)			
< 40	30 (30.0)	101 (24.8)	131 (25.8)
40 – < 65	59 (59.0)	253 (62.2)	312 (61.5)
≥ 65	11 (11.0)	53 (13.0)	64 (12.6)
Race			
White	82 (82.0)	320 (78.6)	402 (79.3)
Black or African American	2 (2.0)	18 (4.4)	20 (3.9)
Asian	15 (15.0)	64 (15.7)	79 (15.6)
Native Hawaiian or other Pacific Islander	1 (1.0)	3 (0.7)	4 (0.8)
Multi race	0	2 (0.5)	2 (0.4)
Weight (kg)			
≤ 100	68 (68.0)	283 (69.5)	351 (69.2)
> 100	32 (32.0)	124 (30.5)	156 (30.8)

Prior exposure to TNF antagonists			
0	65 (65.0)	257 (63.1)	322 (63.5)
≥ 1	35 (35.0)	150 (36.9)	185 (36.5)
Body mass index (kg/m^2)			
< 25	21 (21.0)	72 (17.7)	93 (18.3)
25 – < 30	25 (25.0)	131 (32.2)	156 (30.8)
≥ 30	54 (54.0)	204 (50.1)	258 (50.9)

Baseline disease characteristics

Table 17: Summary of Psoriasis Measures and Body Surface at Baseline, All Randomized Subjects (ITT_A1 Population)

Variable Treatment	N	Mean	SD	Median	Min	Max
PASI (Psoriasis Area and Severity Index)						
PBO	100	21.17	8.682	18.90	12.0	54.2
RZB	407	19.91	7.935	17.20	12.0	63.4
Total	507	20.16	8.094	17.50	12.0	63.4
BSA (Body Surface Area)						
PBO	100	28.3	19.07	23.0	10	90
RZB	407	25.6	17.02	19.0	10	90
Total	507	26.1	17.46	20.0	10	90
NAPSI (Nail Psoriasis Severity Index)						
PBO	96	15.5	17.90	10.0	0	72
RZB	397	12.8	17.98	4.0	0	80
Total	493	13.3	17.98	5.0	0	80
PSSI (Psoriasis Scalp Severity Index)						
PBO	99	19.8	14.67	18.0	0	72
RZB	401	19.5	15.71	16.0	0	72
Total	500	19.6	15.49	16.0	0	72
PPASI (Palmoplantar Psoriasis Area Severity Index)						
PBO	99	3.58	9.127	0.00	0.0	58.0
RZB	401	2.32	6.679	0.00	0.0	48.0
Total	500	2.57	7.237	0.00	0.0	58.0

Max = maximum; Min = minimum; PBO = placebo; RZB = risankizumab; SD = standard deviation

Table 18: sPGA Scores at Baseline, All Randomized Subjects (ITT_A1 Population)

Variable	PBO (N = 100) n (%)	RZB (N = 407) n (%)	Total (N = 507) n (%)
sPGA Categories			
Clear	0	0	0
Almost clear	0	0	0
Mild	0	0	0
Moderate	77 (77.0)	323 (79.4)	400 (78.9)
Severe	23 (23.0)	84 (20.6)	107 (21.1)

PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment

Note: Percentages calculated on non-missing values.

Table 19: Psoriasis Medication History by Therapy Type, All Randomized Subjects (ITT_A1 Population)

Therapy Type	PBO (N = 100) n (%)	RZB (N = 407) n (%)	Total (N = 507) n (%)
Phototherapy or photochemotherapy	39 (39.0)	139 (34.2)	178 (35.1)
Phototherapy	37 (37.0)	129 (31.7)	166 (32.7)
Photochemotherapy	4 (4.0)	22 (5.4)	26 (5.1)
Non-biologic systemic therapy	42 (42.0)	191 (46.9)	233 (46.0)
Any biologics	51 (51.0)	230 (56.5)	281 (55.4)
TNF antagonist	35 (35.0)	150 (36.9)	185 (36.5)
Other biologic (non-TNF antagonist)	40 (40.0)	168 (41.3)	208 (41.0)
Naïve to systemic therapy	32 (32.0)	106 (26.0)	138 (27.2)
Naïve to all (other than topical therapy)	21 (21.0)	70 (17.2)	91 (17.9)

In general demographic parameters were well-balanced across arms.Also baseline disease characteristics were well-balanced between arms. The majority of patients enrolled to this study had moderate psoriasis (79%) and 21% had severe psoriasis as per sPGA score.

Mean PASI score was 21.17 in the placebo group and 19.9 in the risankizumab, mean BSA was 28.3% in the placebo group and 25.6% in the risankizumab group.

55% of patients received biologic therapy before enrolment (36% TNF antagonist and 41% other biologic).These medications were adalimumab, etanercept, infliximab, onercept, abatacept, alefacept, briakinumab, brodalumab, efalizumab, ixekizumab and rituximab.

Part B

Part B (responders to blinded risankizumab re-randomized to either risankizumab (RZB/RZB/RZB) or placebo (RZB/RZB/PBO). **ITT_B_R population**

Two groups:

- RZB/RZB/RZB- responders to blinded risankizumab re-randomized to risankizumab
- RZB/RZB/PBO- responders to blinded risankizumab re-randomized to placebo

399 out of 407 patients originally assigned to risankizumab group in part A entered part B of the study. 336 patents classified as responders were re-randomized to ether placebo (225 subjects) or risankizumab (111 subjects) 63 out of 407 from the original risankizumab group were classified as non-responders. Baseline demographic characteristics of responders who were re-randomized and participated in part B of the study was very similar to the initial study population (part A study). For this population (ITT_B_R Population) mean PASI score was 19.9, BSA was 25% and the majority of subjects (80%) had moderate psoriasis.

As indicated above 63 patients did not respond to risankizumab at entry of Part B and were included in the ITT_B_NR Population. It seems that in the group of non-responders more patients had severe psoriasis at baseline (27%) as compared to 19 % in the responders group and there were more females in this group. In addition mean weight was slightly higher at baseline in the non-responses group.

- **Numbers analysed**

It is noted that 40 patients in the placebo-re-randomised group received rescue therapy whereas only 3 such patients were in the risankizumab re-randomised group.

- **Outcomes and estimation**

Part A

Primary endpoints

There were 2 co-primary endpoints in this study w.g achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16 and achievement of an sPGA score of clear or almost clear (0 or 1) at Week 16.

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 placebo group. See the table below.

Table 20: Co-Primary Endpoints in Part A: Proportions of Subjects with PASI 90 and sPGA Clear or Almost Clear at Week 16, NRI (ITT_A1 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)					

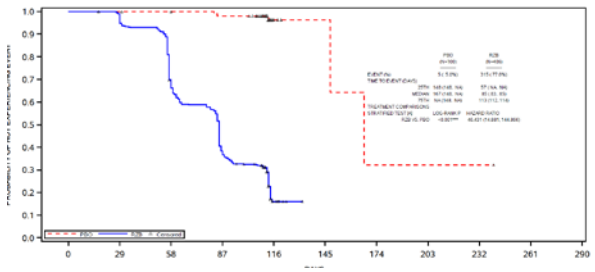
CI = confidence interval; Diff = difference; ITT = Intent-to-Treat; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment

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.

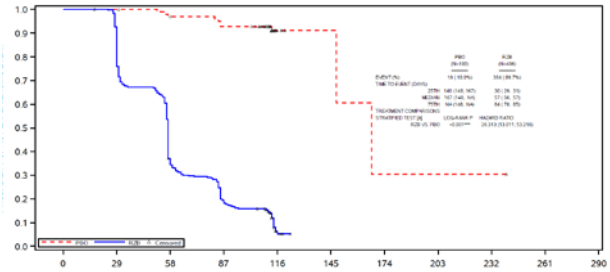
b. Across the strata, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata. Within each stratum, *P* value was calculated based on the chi-square test (or Fisher's exact test if ≥ 25% of the cells had expected cell count < 5).

Figure 4: Time to first achievement a) in PASI 90 b) sPGA

a)



b)



Pre-specified subgroups analysis

In the study the following subgroups were pre-specified and analysed:

- Age group (< 40 years, ≥ 40 – < 65 years, ≥ 65 years)
- Sex (male, female)
- Race (white, non-white)
- Smoking (current, ex or never)
- BMI (normal: < 25, over weight: ≥ 25 – < 30, obese: ≥ 30)
- Region (US, Asia, Other)
- Baseline PASI score (by median)
- Baseline sPGA (3, 4)
- Psoriatic arthritis (yes [diagnosed or suspected], no)
- Psoriasis Therapy History (Phototherapy or Photochemotherapy, TNF Antagonist, Other biologics, Non-biologic systemic therapy, All biologics, Naïve to all)

Treatment effects in all pre-specified subgroups were in favor of risankizumab for PASI 90 and sPGA clear or almost clear.

Secondary endpoints for part A

Risankizumab was statistically significantly superior to placebo for all ranked secondary endpoints for assessments done at week 16 (ITT_A1 Population).

Table 21: Statistical Results for Ranked Secondary Endpoints in Part A Presented in Rank Order (ITT_A1 Population)

Ranked Secondary Variable	PBO n/N (%)	RZB n/N (%)	Adjusted Difference %	*P* value[a]
1. Proportion of subjects who achieved PASI 75 at Week 16	8/100 (8.0)	361/407 (88.7)	80.6	< 0.001
2. Proportion of subjects who achieved PASI 100 at Week 16	1/100 (1.0)	192/407 (47.2)	45.5	< 0.001
3. Proportion of subjects who achieved sPGA of clear at Week 16	1/100 (1.0)	189/407 (46.4)	44.8	< 0.001
4. Proportion of subjects who achieved DLQI 0/1 at Week 16	3/100 (3.0)	266/407 (65.4)	62.1	< 0.001

DLQI = Dermatology Life Quality Index; ITT = Intent-to-Treat; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment

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).

Statistically significantly larger proportions of subjects in the risankizumab group achieved PASI 90, PASI 100, and sPGA clear or almost clear at all visits during Part A1 compared with the placebo group.

Table 22: Proportions of Subjects Who Achieved PASI 90, PASI 100, and sPGA Clear or Almost Clear at Weeks 4, 8, 12, and 16, Part A1 (ITT_A1 Population)

Visit	PBO n/N (%)	RZB n/N (%)	Adjusted Difference %	95% CI[a]	*P* value[b]
PASI 90					
Week 4	0/100	29/407 (7.1)	6.9	4.1, 9.7	< 0.001
Week 8	0/100	165/407 (40.5)	40.0	35.1, 45.0	< 0.001
Week 12	2/100 (2.0)	270/407 (66.3)	63.9	58.5, 69.4	< 0.001
Week 16	2/100 (2.0)	298/407 (73.2)	70.8	65.7, 76.0	< 0.001
PASI 100					
Week 4	0/100	9/407 (2.2)	2.0	0.0, 3.9	0.046
Week 8	0/100	87/407 (21.4)	21.0	16.8, 25.1	< 0.001
Week 12	1/100 (1.0)	162/407 (39.8)	38.4	33.1, 43.6	< 0.001
Week 16	1/100 (1.0)	192/407 (47.2)	45.5	40.3, 50.8	< 0.001
sPGA clear or almost clear					
Week 4	0/100	134/407 (32.9)	32.5	27.8, 37.2	< 0.001
Week 8	3/100 (3.0)	277/407 (68.1)	64.8	59.1, 70.4	< 0.001
Week 12	6/100 (6.0)	326/407 (80.1)	73.9	67.8, 79.9	< 0.001
Week 16	7/100 (7.0)	340/407 (83.5)	76.5	70.4, 82.5	< 0.001

CI = confidence interval; ITT = Intent-to-treat; 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. 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).

Statistically significant differences were observed between the risankizumab and placebo groups during Part A1 on measures of improvement of PsA (changes from Baseline in TJC, SJC, DAS28, and HAQ-DI), nail psoriasis (NAPSI), palmoplantar psoriasis (PPASI), and scalp psoriasis (PSSI) at Week 16.

Among subjects with confirmed PsA, the risankizumab group had a statistically significantly greater mean reduction (–0.532 in Disability Index of the Health Assessment Questionnaire [HAQ-DI] score at Week 16 compared with subjects in the placebo group (–0.138). In addition, larger proportions of subjects in the risankizumab group achieved a reduction ≥ 0.3 points in the HAQ-DI compared with the placebo group (45.2% versus 25.0%); however, the difference was not statistically significant due to the small sample size (31 subjects in the risankizumab and 12 subjects in the placebo groups).

In subjects with confirmed PsA, the risankizumab group had a statistically significantly greater mean change in tender joint count (TJC) (–3.4) compared with the placebo group (–0.9) at Week 16. The risankizumab group also had a statistically significantly greater mean change in swollen joint count (SJC) (–3.6) compared with the placebo group (0.7) at Week 16.

Significantly better results as compared to placebo were achieved also for The Dermatology Life Quality Index (no impairment):

Table 23: Proportion of subjects achieving a DLQI 0 or 1 (NRI) by visit of part A1

VISIT	STRATA	TREATMENT	N	YES n	YES %	NO n	NO %	MISSING n	MISSING %	DIFF %	ADJUSTED DIFF %	95 % CI [A]	P-VALUE [B]
WEEK 12													
	ALL												<0.001***
		PBO	100	2	(2.0)	93	(93.0)	5	(5.0)				
		RZB	407	243	(59.7)	158	(38.8)	6	(1.5)	57.7	57.4	(51.9, 63.0)	
WEEK 16													
	ALL												<0.001***
		PBO	100	3	(3.0)	91	(91.0)	6	(6.0)				
		RZB	407	266	(65.4)	133	(32.7)	8	(2.0)	62.4	62.1	(56.4, 67.9)	

NOTE: STRATA: WEIGHT (<= 100 KG VS > 100 KG) AND PRIOR EXPOSURE TO TNF ANTAGONISTS (0 VS >= 1).
PBO: SUBJECTS RANDOMIZED TO PLACEBO IN PART A; RZB: SUBJECTS RANDOMIZED TO RISANKIZUMAB IN PART A.
[A]: ACROSS THE STRATA, 95% CI FOR ADJUSTED DIFFERENCE WAS CALCULATED ACCORDING TO THE COCHRAN-MANTEL-HAENSZEL TEST FOR THE COMPARISON OF TWO TREATMENT GROUPS. IF THERE IS A STRATUM CONTAINING ZERO COUNT, 0.1 WILL BE ADDED TO EACH CELL. 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. IF THERE IS A STRATUM CONTAINING ZERO COUNT, 0.1 WILL BE ADDED TO EACH CELL. WITHIN EACH STRATUM, P-VALUE WAS CALCULATED BASED ON CHI-SQUARE TEST (OR FISHER'S EXACT TEST IF >= 25% OF THE CELLS HAVE EXPECTED CELL COUNT < 5).
FOR COMPARISONS: ***, **, * STATISTICALLY SIGNIFICANT AT THE 0.001, 0.01, 0.05 LEVEL, RESPECTIVELY.

Part B

Primary endpoint

Part B – Re-Randomized Subjects -(ITT_B_R) population: All subjects who were randomized to Arm 1 at Baseline and re-randomized at Week 28

In the statistical plan the proportion of re-randomized subjects who achieved sPGA of clear or almost clear at Week 52 was pre-specified as a primary endpoint for part B of the study.

In the study the primary endpoint for Part B was also achieved. A statistically significantly larger proportion of subjects who were re-randomized to continue risankizumab treatment in Part B achieved sPGA clear or almost clear at Week 52 compared with subjects who were withdrawn from risankizumab therapy (re-randomized to placebo).

Of note, subjects who discontinued due to AE of "Worsening of disease under study," or received retreatment with risankizumab for relapse during Part B, were counted as nonresponders in all visits thereafter in the NRI and MI analyses, and will have their last observation prior to discontinuation or retreatment with risankizumab carried forward in the LOCF analyses."

Table 24: Proportion of Re-Randomized Subjects Who Achieved sPGA of Clear or Almost Clear at Week 52, NRI (ITT_B_R Population)

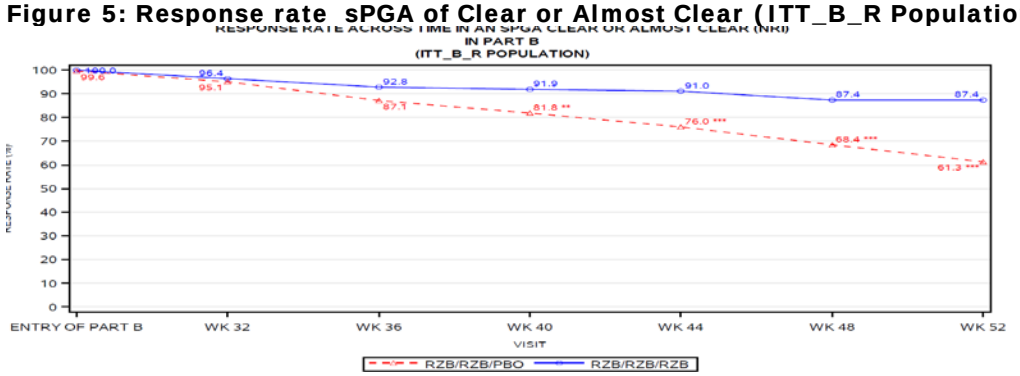
		Yes		No		Missing			Adjusted			Breslow-Day
Treatment	N	n	%	n	%	n	%	Diff %	Diff %	95% CI[a]	*P* value[b]	*P* value
RZB/RZB/PBO	225	138	(61.3)	49	(21.8)	38	(16.9)	26.1	25.9	(17.3, 34.6)	<0.001	0.175
RZB/RZB/RZB	111	97	(87.4)	6	(5.4)	8	(7.2)					

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).

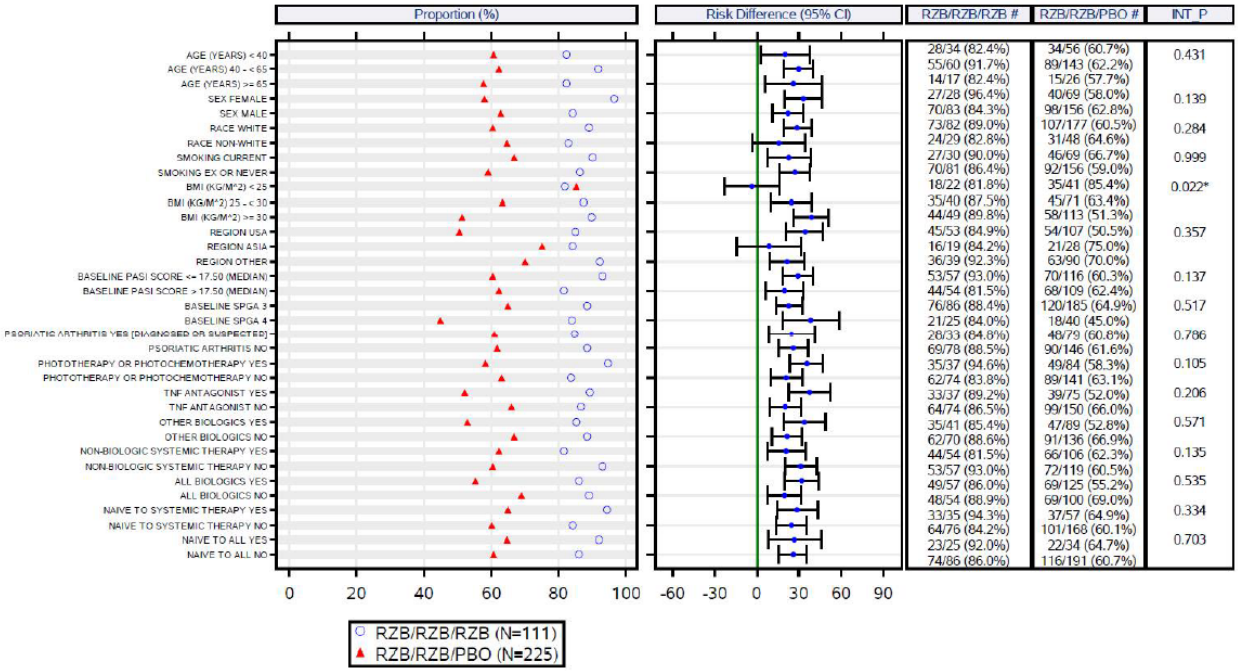
Figure 5: Response rate_sPGA of Clear or Almost Clear (ITT_B_R Population)



Pre-specified subgroups analysis

Among subjects re-randomized to placebo or risankizumab, treatment effects in prespecified subgroups were in favor of risankizumab with 95% confidence intervals of the treatment difference excluding zero in the vast majority of the subgroups for sPGA clear or almost clear.

Table 25: Proportion of Re-Randomized Subjects With sPGA of Clear or Almost Clear at Week 52, by Subgroup, NRI (ITT_B_R Population)



BMI = body mass index; CI = confidence interval; ITT = Intent-to-Treat; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment; TNF = tumor necrosis factor

***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively.

Note: INT_P is the *P* value for treatment-subgroup interaction.

Secondary endpoints for part B

Among Week 28 risankizumab responders who were re-randomized to continue risankizumab treatment or to withdraw from risankizumab treatment (placebo), statistically significant differences in favor of risankizumab were observed in proportions of subjects who achieved PASI 75, PASI 90, and PASI 100 at Week 52.

Response rates for PASI 90, PASI 100 and sPGA of clear in re-randomized subjects supported the primary endpoint results (sPGA of clear or almost clear) for Part B. Statistically significantly larger proportions of subjects who were re-randomized to continue risankizumab treatment achieved those responses compared with subjects withdrawn from risankizumab treatment (placebo).

Table 26: Statistical Results for Other Secondary Endpoints in Subjects Who Were Re-Randomized in Part B, NRI (ITT_B_R Population)

Ranked Secondary Variable	RZB/RZB/PBO n/N (%)	RZB/RZB/RZB n/N (%)	% Diff	*P* value[a]
1. Proportion of subjects who achieved PASI 75 at Week 52	161/225 (71.6)	103/111 (92.8)	21.2	< 0.001
2. Proportion of subjects who achieved PASI 90 at Week 52	118/225 (52.4)	95/111 (85.6)	33.1	< 0.001
3. Proportion of subjects who achieved PASI 100 at Week 52	68/225 (30.2)	71/111 (64.0)	33.7	< 0.001

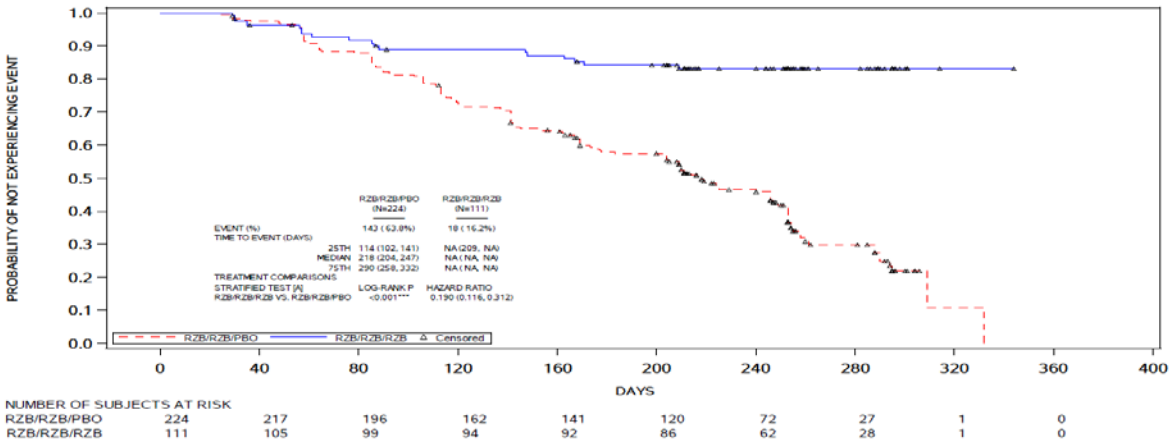
Diff = difference; ITT = Intent-to-Treat; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab

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).

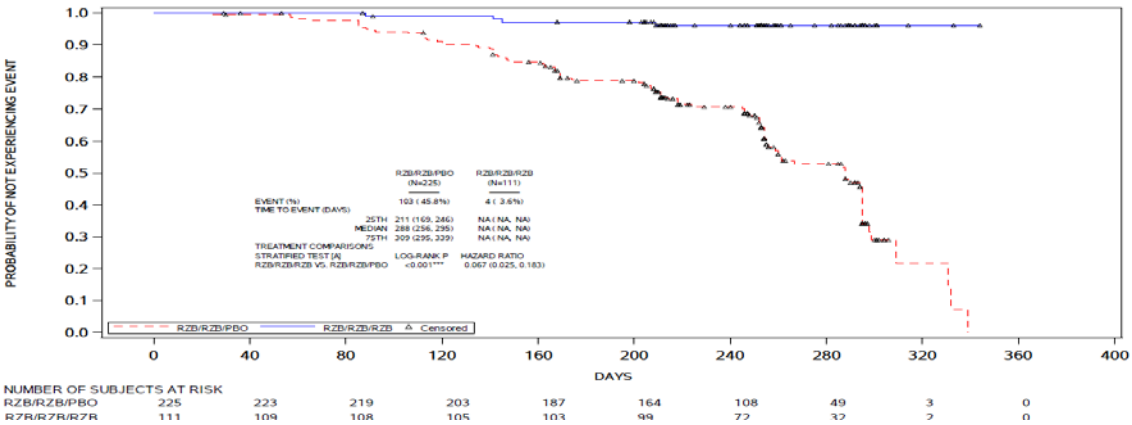
Time until loss of response and time until sPGA score of ≥ 3 (relapse)

The interim analysis of data was performed before many subjects had lost response; therefore, a large number of subjects were censored by the cutoff date. However, the Kaplan-Meier curves showed a clear separation between the 2 treatment groups indicating a faster loss of response among subjects who were re-randomized to withdrawal from the treatment.

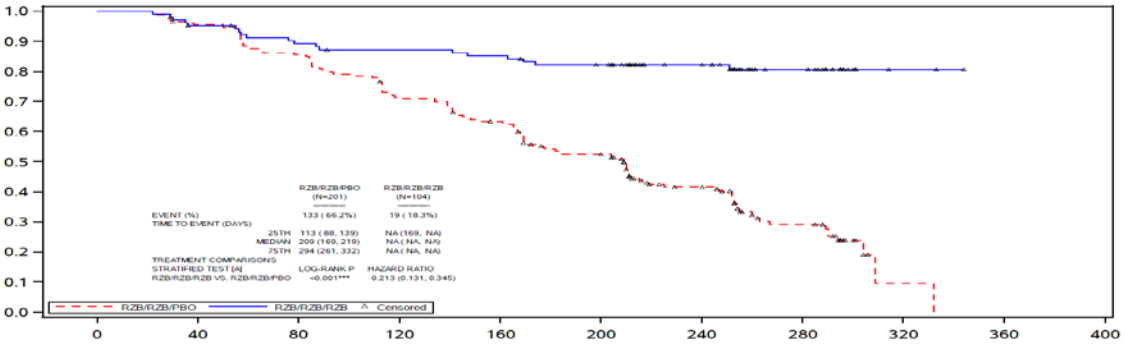
- **Time until loss of sPGA of 0 or 1 response for patients re-randomised at Week 28**



- **Time until sPGA score of ≥ 3 (relapse) for patients re-randomised at Week 28**



- **Time until loss of PASI 90 in part B among subjects who achieved PASI 90 at week 28**



Subjects with confirmed Pasi

and selected for PsA assessment.

Part B – Re-Treatment After Withdrawal- ITT_B_PBO_RT population, All subjects who were re-randomized to placebo and received at least one dose of re-treatment with open-label risankizumab after relapse, and had the opportunity to have re-treatment Week 16 assessments.

This population included 40 patients

Of 40 sPGA responders at Week 28 who were re-randomized to withdrawal (placebo) in Part B, relapsed (sPGA ≥ 3), and had at least 1 dose of risankizumab re-treatment at least 16 weeks prior to the re-treatment data cut-off (22 September 2017), 85% (34/40) regained sPGA of clear or almost clear.

Twenty-six subjects (65.0%) achieved PASI 90 at Week 16 of re-treatment

Table 27: proportion of subjects achieving PASI 90 By visit of retreatment cohort 1

VISIT	STRATA	TREATMENT	N	YES n	YES %	NO n	NO %	MISSING n	MISSING %
WEEK 16R									
	ALL								
		RZB/RZB/PBO/RZB	40	26	(65.0)	14	(35.0)	0	
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB/PBO/RZB	12	8	(66.7)	4	(33.3)	0	
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB/PBO/RZB	6	4	(66.7)	2	(33.3)	0	
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB/PBO/RZB	13	9	(69.2)	4	(30.8)	0	
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB/PBO/RZB	9	5	(55.6)	4	(44.4)	0	

Part B – Risankizumab Re-Load

Only 3 subjects who were re-randomized to continue risankizumab treatment relapsed and received a loading dose at least 16 weeks prior to the re-treatment data cut-off (22 September 2017); therefore, no conclusions were drawn.

Part B – Non-Responders in Part A, ITT_B_NR Population= All subjects who were randomized to Arm 1 at Baseline, were non-responders (sPGA ≥ 2) at Week 28, and received at least one dose of risankizumab on or after Week 28.

This population included 63 subjects

Of the subjects who were randomized to risankizumab at Baseline and did not achieve sPGA clear or almost clear at Week 28 (non-responders), 38.1% achieved sPGA clear or almost clear at Week 32, and 49.2% achieved sPGA clear or almost clear at Week 52.

Part A2 population ITT_A2 All subjects who were randomized to Arm 1 at Baseline

Small improvements in PASI 90 and sPGA clear or almost clear was observed from week 16 to week 28 in A2 group.

Table 28: Proportion of subjects achieving PASI 90 by visit of part A2 at study entry, and at week 28

VISIT	STRATA	TREATMENT	N	YES n	YES %	NO n	NO %	MISSING n	MISSING %
ENTRY OF PART A2									
	ALL								
		RZB/RZB	407	300	(73.7)	106	(26.0)	1	(0.2)
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB	192	148	(77.1)	44	(22.9)	0	
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB	65	44	(67.7)	20	(30.8)	1	(1.5)
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB	91	67	(73.6)	24	(26.4)	0	
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB	59	41	(69.5)	18	(30.5)	0	
WEEK 28									
	ALL								
		RZB/RZB	407	312	(76.7)	83	(20.4)	12	(2.9)
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB	192	148	(77.1)	38	(19.8)	6	(3.1)
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB	65	51	(78.5)	12	(18.5)	2	(3.1)
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB	91	69	(75.8)	20	(22.0)	2	(2.2)
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB	59	44	(74.6)	13	(22.0)	2	(3.4)

Table 29: Proportion of subjects achieving an sPGA clear or almost clear by visit of part A2 at study entry, and at week 28

VISIT	STRATA	TREATMENT	N	YES n	YES %	NO n	NO %	MISSING n	MISSING %
ENTRY OF PART A2									
	ALL								
		RZB/RZB	407	342	(84.0)	64	(15.7)	1	(0.2)
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB	192	171	(89.1)	21	(10.9)	0	
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB	65	53	(81.5)	11	(16.9)	1	(1.5)
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB	91	70	(76.9)	21	(23.1)	0	
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB	59	48	(81.4)	11	(18.6)	0	
WEEK 28									
	ALL								
		RZB/RZB	407	337	(82.8)	59	(14.5)	11	(2.7)
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB	192	165	(85.9)	21	(10.9)	6	(3.1)
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS = 0								
		RZB/RZB	65	56	(86.2)	7	(10.8)	2	(3.1)
	BASELINE WEIGHT <= 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB	91	71	(78.0)	18	(19.8)	2	(2.2)
	BASELINE WEIGHT > 100 KG AND PRIOR EXPOSURE TO TNF ANTAGONISTS >= 1								
		RZB/RZB	59	45	(76.3)	13	(22.0)	1	(1.7)

2.5.2.4. Study M15-997 (1311.31)

Title: A Multicenter, Open Label Study to Assess the Safety and Efficacy of Risankizumab for Maintenance in Moderate to Severe Plaque Type Psoriasis

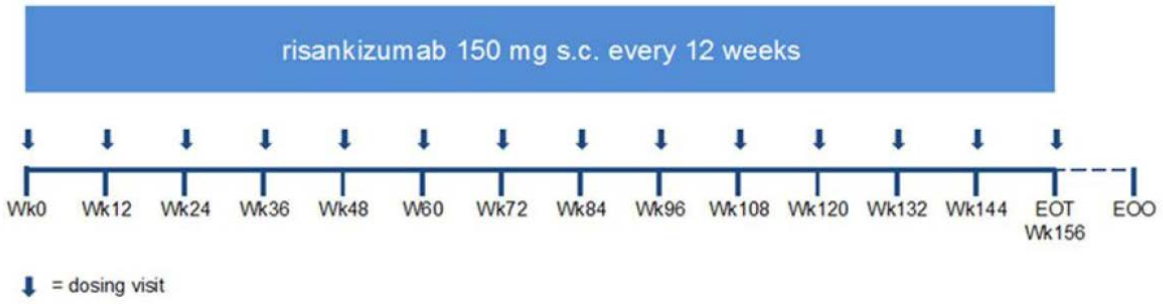
- **Methods:**

This Phase 3, single-arm, multicenter, OLE study was designed to investigate the long-term safety and efficacy of risankizumab 150 mg administered every 12 weeks in the treatment of moderate to severe chronic plaque psoriasis. Approximately 2000 subjects who meet the entry criteria were planned to be enrolled in this study, rolling over from the lead-in Studies M16-008, M15-992, M15-995, M16-010, M16-004, and M16-178 (Phase 2/3, randomized clinical studies in subjects with moderate to severe chronic plaque psoriasis conducted by AbbVie or BI).

To enter Study M15-997, all subjects must have completed 1 of the lead-in Phase 2/3 psoriasis studies. Subjects preferably have the baseline visit of Study M15-997 on the same day as the completion visit of the lead-in study; however, the Baseline visit can be delayed up to 8 weeks, if needed.

Study visits for dosing and efficacy and safety assessments are performed every 12 weeks starting from baseline until the end of Treatment Visit at Week 156,

Figure 6: Study Design Schematic



- **Study participants**

Main Inclusion:

- Subjects with moderate to severe chronic plaque psoriasis who have completed one of the preceding Studies 1311.3, 1311.4, 1311.28, 1311.30, 1311.38 and M16-178.
- Subjects must be candidates for prolonged open label risankizumab treatment according to investigator judgment.

Main Exclusion:

- Premature discontinuation for any reason in the preceding study.

- **Treatments**

All subjects were to receive subcutaneous injections of risankizumab as 2 prefilled syringes of 75 mg each (150 mg total) at each dosing visit (every 12 weeks).

This is an open-label study, and the treatment is the same for all subjects. Investigational devices or products

The following treatments were not allowed.

- Anti-IL-12/23, and anti-IL-17 agents, including but not limited to guselkumab, tildrakizumab, ustekinumab, ixekizumab and secukinumab; only comparator drug use in previous study is allowed for ustekinumab
- TNF inhibitors; only comparator drug use in preceding study is allowed for Adalimumab (Humira®)
- Topical treatment for psoriasis or any other skin condition such as retinoids, vitamin D analogues, vitamin A analogs, anthralin and steroids. Exception: Topical steroids may be used (US class 6 or 7) for limited period of time following consultation with Abbvie TA MD without removing subjects from the study with a restriction of use within 24 hours prior to study visit
- Systemic immunomodulating medications including methotrexate (MTX), cyclosporine A and corticosteroids except steroids with only a topical effect
- Systemic psoriasis medications including retinoids and fumarates, or any other drugs known to possibly benefit psoriasis
- Photochemotherapy (e.g., PUVA)
- Phototherapy (e.g., UVA, UVB, Ultra Violet A/B)
- **Outcomes/endpoints**

Key variables to be summarized at all visits:

- Proportion of subjects achieving ≥ 90% reduction in Psoriasis Area and Severity Index (PASI) score (PASI 90)
- Proportion of subjects achieving the Static Physician Global Assessment (sPGA) score of clear or almost clear
- Proportion of subjects achieving ≥ 75% reduction in PASI score (PASI 75)
- Proportion of subjects achieving 100% reduction in PASI score (PASI 100)
- Proportion of subjects achieving the sPGA score of clear
- **Statistical methods**

As Study M15-997 is an OLE study, no statistical tests were planned for the analyses of efficacy. Summary statistics were provided.

Results

Baseline data

Table 30: Baseline Characteristics – PASI, BSA, NAPSI, PSSI, and PPASI (UST_RZB and ADA_RZB Populations)

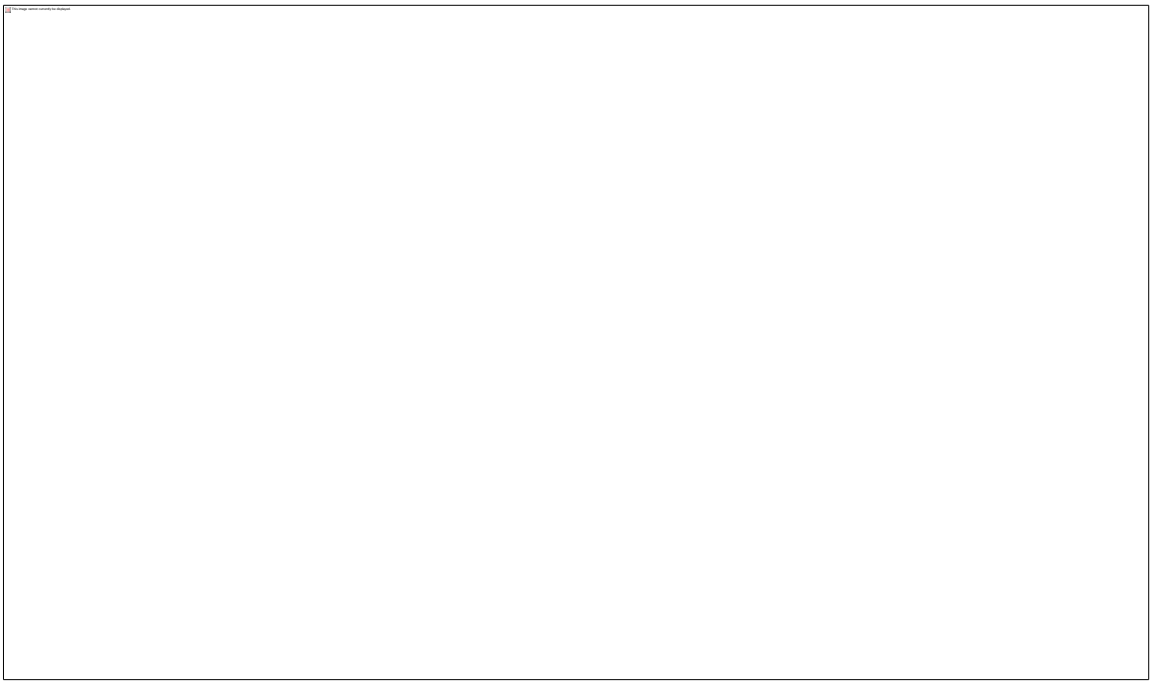


Table 31: Baseline Disease Characteristics – sPGA (UST_RZB and ADA_RZB Populations)

Variable	UST RZB (N = 169) n (%)	ADA RZB (N = 260) n (%)
sPGA Categories		
Moderate	139 (82.2)	212 (81.5)
Severe	30 (17.8)	48 (18.5)

ADA = adalimumab; RZB = risankizumab; sPGA = static Physician Global Assessment; UST = ustekinumab

Number analysed

For this interim CSR, 3 populations were included in the analyses: the Ustekinumab-to- Risankizumab (UST_RZB), Adalimumab-to-Risankizumab (ADA_RZB), and All Risankizumab-Treated (ALL_RZB) Populations

Table 32: Data Sets and Treatment Groups Analyzed in the Study M15-997 Interim CSR

Population	Definition	N
UST_RZB	Subjects who were randomized to UST in Studies M16-008 (1311.3) and M15-995 (1311.28). This population is used to assess the efficacy and safety of RZB when subjects switch from UST to RZB in both the interim and final CSRs.	169
ADA_RZB	Subjects who were randomized to ADA in Study M16-010 (1311.30). This population is used to assess the efficacy and safety of RZB when subjects switch from ADA to RZB in both the interim and final CSRs.	260
Re-rand to RZB	Subjects re-randomized to RZB at entry of Part B in Study M16-010 who received RZB in Study M15-997	48
B_NR	Adalimumab nonresponders (subjects who did not achieve PASI 50) who switched from ADA to RZB at entry of Part B in Study M16-010 and received RZB in Study M15-997	33
Re-rand to ADA	Subjects re-randomized to adalimumab at entry of Part B in Study M16-010 who switched from ADA to RZB in Study M15-997	49
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	130
ALL_RZB	All subjects who received at least 1 dose of RZB in Study M15-997. This population is used for additional safety analyses.	1392

ADA = adalimumab; CSR = clinical study report; PASI 50/90 = ≥ 50%/90% reduction in Psoriasis Area and Severity Index score; RZB = risankizumab; UST = ustekinumab

For the UST_RZB Population, all subjects switched from ustekinumab to risankizumab at entry of Study M15-997. Therefore, efficacy and safety results from all subjects are presented in the text of this interim report.

For the ADA_RZB Population, subjects in 2 treatment groups switched from adalimumab to risankizumab at entry of Study M15-997:

- Subjects who were re-randomized to adalimumab at entry of Part B in Study M16-010 who switched from adalimumab to risankizumab in Study M15-997 (denoted in this report as subjects re-randomized to adalimumab in Study M16-010 [in text] or Re-randomized to adalimumab [in tables])
- 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 (denoted in this report as adalimumab responders [in text] or B_R [in tables])

This interim CSR does not include analyses of the following 3 additional populations described in the SAP, which will be used for efficacy analyses in the final CSR and are presented in the Integrated Summary of Efficacy:

RZB Population: This population consists of subjects who were randomized to risankizumab in Studies M16-008 (1311.3), M16-010 (1311.30), M15-995 (1311.28), and M16-178. This population will be used to evaluate the long term efficacy of risankizumab with a loading dose.

RZB_NL Population: This population consists of subjects who were randomized to placebo in the lead-in study and continued to risankizumab (without a loading dose) in Studies M16-008 (1311.3), M15-992 (1311.4), and M15-995 (1311.28). This population will be used to evaluate the long-term efficacy of risankizumab without an initial loading dose.

Re-treatment Population: This population consists of subjects who were rerandomized to placebo in Part B of Study M15-992 (1311.4). This population will be used to evaluate the efficacy of re-treatment after temporary withdrawal.

Table 33: Baseline Characteristics – PASI, BSA, NAPSI, PSSI, and PPASI (UST_RZB and ADA_RZB Populations)

Variable Treatment	N	Mean	SD	Median	Min	Max
PASI						
UST_RZB	169	19.03	5.948	17.70	12.1	44.0
ADA_RZB	260	19.61	7.246	17.75	12.0	47.4
BSA						
UST_RZB	169	22.8	12.85	19.0	10	70
ADA_RZB	260	25.5	16.54	20.0	10	85
NAPSI						
UST_RZB	164	13.0	19.08	4.0	0	80
ADA_RZB	260	17.9	20.64	11.0	0	80
PSSI						
UST_RZB	167	16.5	13.51	12.0	0	72
ADA_RZB	260	19.5	16.29	18.0	0	72
PPASI						
UST_RZB	167	1.76	5.821	0.00	0.0	54.0
ADA_RZB	260	1.77	5.280	0.00	0.0	46.8

ADA = adalimumab; BSA = Body Surface Area; Max = maximum; Min = minimum; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PPASI = Palmoplantar Psoriasis Area and Severity Index; PSSI = Psoriasis Scalp Severity Index; RZB = risankizumab; SD = standard deviation; UST = ustekinumab

Table 34: Baseline Disease Characteristics – sPGA (UST_RZB and ADA_RZB Populations)

Variable	UST RZB (N = 169) n (%)	ADA RZB (N = 260) n (%)
sPGA Categories		
Moderate	139 (82.2)	212 (81.5)
Severe	30 (17.8)	48 (18.5)

ADA = adalimumab; RZB = risankizumab; sPGA = static Physician Global Assessment; UST = ustekinumab

Outcomes and estimation

As Study M15-997 is an OLE study, no statistical tests were planned for the analyses of efficacy. Summary statistics were provided.

- **Patients on ustekinumab and switched to risankizumab**

Table 35: Proportion of PASI and sPGA Responders After Switching to Risankizumab at Entry to Study M15-997 by Visit (LOCF, UST_RZB Population)

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

LOCF = last observation carried forward; OLE = open-label extension; PASI 75/90/100 = ≥ 75%/90%/100% reduction in Psoriasis Area and Severity Index score; RZB = risankizumab; sPGA = Static Physician Global Assessment; UST = ustekinumab

At week 24 similar good results were achieved in this subpopulation.

- **Patients on adalimumab and switched to risankizumab**

Among subjects who completed M16-010 (1311.30) study on adalimumab and were switched to risankizumab in Study M15-997, the proportions of subjects who achieved sPGA clear or almost clear, sPGA clear, PASI 90, PASI 100, and PASI 75 increased at Week 12.

The efficacy data were also provided for subgroups within the ADA_RZB population.

- **B_R group (adalimumab responders) and Re-randomized to ADA (adalimumab) group**

Table 37 Proportion of PASI Responders After Switching to Risankizumab at Entry to Study M15-997 by Visit (LOCF, ADA_RZB Population)

		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	Treatment	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Entry of OLE	RZB	49	28 (57.1)	130	117 (90.0)	49	11 (22.4)	130	95 (73.1)	49	3 (6.1)	130	68 (52.3)
Week 12	RZB	27	25 (92.6)	64	63 (98.4)	27	21 (77.8)	64	59 (92.2)	27	9 (33.3)	64	50 (78.1)

ADA = adalimumab; LOCF = last observation carried forward; OLE = open-label extension; PASI 75/90/100 = ≥ 75%/90%/100% reduction in Psoriasis Area and Severity Index score; RZB = risankizumab

Note: Re-rand to ADA: Subjects re-randomized to 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.

Table 36: Proportion of sPGA Responders After Switching to Risankizumab at Entry to Study M15-997 by Visit (LOCF, ADA_RZB Population)

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

ADA = adalimumab; LOCF = last observation carried forward; OLE = open-label extension; PASI 90 = ≥ 90% reduction in Psoriasis Area and Severity Index score; RZB = risankizumab; sPGA = Static Physician Global Assessment

Note: Re-rand to ADA: Subjects re-randomized to 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.

- **B_NR group, (adalimumab nonresponders)" and Re-randomized to RZB group**

Table 37: Proportion of subjects achieving PASI 90 (locf) by visit (ADA_RZB population)

PASI 50 NON-RESPONDERS AT ENTRY OF PART B

VISIT	TREATMENT	N	YES n	YES %	NO n	NO %
SWITCH TO RZB	RZB	33	0		33	(100)
WEEK 4S	RZB	33	0		33	(100)
WEEK 8S	RZB	33	4	(12.1)	29	(87.9)
WEEK 12S	RZB	33	14	(42.4)	19	(57.6)
WEEK 16S	RZB	33	18	(54.5)	15	(45.5)
WEEK 20S	RZB	33	21	(63.6)	12	(36.4)
WEEK 24S	RZB	33	23	(69.7)	10	(30.3)
WEEK 28S	RZB	33	24	(72.7)	9	(27.3)
WEEK 40S	RZB	33	25	(75.8)	8	(24.2)
WEEK 52S	RZB	33	25	(75.8)	8	(24.2)

RE-RANDOMIZED TO RZB AT ENTRY OF PART B

VISIT	TREATMENT	N	YES n	YES %	NO n	NO %
SWITCH TO RZB	RZB	48	0		48	(100)
WEEK 4S	RZB	47	25	(53.2)	22	(46.8)
WEEK 8S	RZB	48	29	(60.4)	19	(39.6)
WEEK 12S	RZB	48	33	(68.8)	15	(31.3)
WEEK 16S	RZB	48	34	(70.8)	14	(29.2)
WEEK 20S	RZB	48	34	(70.8)	14	(29.2)
WEEK 24S	RZB	48	32	(66.7)	16	(33.3)
WEEK 28S	RZB	48	33	(68.8)	15	(31.3)
WEEK 40S	RZB	48	32	(66.7)	16	(33.3)
WEEK 52S	RZB	48	32	(66.7)	16	(33.3)

Table 38: Proportion of subjects achieving sPGA clear or almost clear (locf) by visit (ADA_RZB population)

PASI 50 NON-RESPONDERS AT ENTRY OF PART B

VISIT	TREATMENT	N	YES n	YES %	NO n	NO %
SWITCH TO RZB	RZB	33	0		33	(100)
WEEK 4S	RZB	33	9	(27.3)	24	(72.7)
WEEK 8S	RZB	33	19	(57.6)	14	(42.4)
WEEK 12S	RZB	33	20	(60.6)	13	(39.4)
WEEK 16S	RZB	33	21	(63.6)	12	(36.4)
WEEK 20S	RZB	33	25	(75.8)	8	(24.2)
WEEK 24S	RZB	33	26	(78.8)	7	(21.2)
WEEK 28S	RZB	33	25	(75.8)	8	(24.2)
WEEK 40S	RZB	33	25	(75.8)	8	(24.2)
WEEK 52S	RZB	33	25	(75.8)	8	(24.2)

RE-RANDOMIZED TO RZB AT ENTRY OF PART B

VISIT	TREATMENT	N	YES n	YES %	NO n	NO %
SWITCH TO RZB	RZB	48	22	(45.8)	26	(54.2)
WEEK 4S	RZB	47	31	(66.0)	16	(34.0)
WEEK 8S	RZB	48	37	(77.1)	11	(22.9)
WEEK 12S	RZB	48	41	(85.4)	7	(14.6)
WEEK 16S	RZB	48	37	(77.1)	11	(22.9)
WEEK 20S	RZB	48	39	(81.3)	9	(18.8)
WEEK 24S	RZB	48	39	(81.3)	9	(18.8)
WEEK 28S	RZB	48	36	(75.0)	12	(25.0)
WEEK 40S	RZB	48	40	(83.3)	8	(16.7)
WEEK 52S	RZB	48	40	(83.3)	8	(16.7)

Quality of Life Results

Improvements in the DLQI were seen in all treatments groups (switched from ustekinumab and switched from adalimumab). The median baseline DLQI score was 13.0.

Efficacy and Antibodies to Risankizumab

Immunogenicity of risankizumab was assessed using a 3-tiered approach. In this tiered approach, all anti-drug antibody samples were first analysed in a screening assay (Tier 1). The samples that were screened positive were confirmed in the confirmatory assay (Tier 2) followed by the titer determination step (Tier 3) in which titers were determined for the confirmed positive samples. The confirmed positive samples were also evaluated in the NAb assay to detect the presence of NAbs.

For immunogenicity assessment, the evaluable subjects (subjects with at least 1 reportable immunogenicity assessment for at least 1 sampling time during the study postbaseline) were used to calculate the anti-drug antibody (treatment emergent) or NAb incidence.

Incidence of anti-drug antibody (treatment emergent) to risankizumab was defined when a subject was (1) anti-drug antibody-negative or missing assessment at baseline (prior to first risankizumab dose) and became anti-drug antibody-positive at 1 or more time points postbaseline, or (2) anti-drug antibody-positive at baseline and showed a 4-fold or greater increase in titer values relative to baseline or a titer value of 2 or greater in at least 1 post-dose sample if the baseline titer value was less than 1 (in this case 4-fold increment over midpoint of 0.5 was used).

The time to first appearance of anti-drug antibody was also calculated among the antidrug antibody (treatment emergent) positive subjects using actual time following the first dose of risankizumab for subjects who received at least 1 dose of risankizumab in the study.

The ADA and NAb to risankizumab across Phase 1 – 3 studies in subjects with psoriasis were characterized as follows:

- In the Phase 1 single-dose study (Study 1311.1), ADA incidence (treatment emergent) was 11% (2/18) and 0% (0/13) following single IV and SC risankizumab doses, respectively.
- In the Phase 1 therapeutic protein-drug interaction study (Study M16-007 [1311.36]); ADA incidence (treatment-emergent) was 24% (5/21 of subjects) following administration of risankizumab 150 mg SC doses every 4 weeks.
- In the Phase 2 study (Study 1311.2), ADA and NAb incidence (treatment emergent) were 14.5% (18/124) and 3.2% (4/124) following SC dosing with risankizumab over 48 week duration.
- For subjects who received the proposed clinical regimen of risankizumab in psoriasis (150 mg at Week 0, Week 4, and q12w thereafter) in Phase 3 trials:
  - The anti-drug antibody and NAb incidence (treatment emergent) to risankizumab was 19% and 8%, respectively over 16 weeks duration (based on 1288 evaluable subjects) and 24% and 14% respectively over 52 weeks duration (based on 1079 evaluable subjects).
  - The median time to appearance of ADA was 16 weeks across studies.

A total of 16 subjects (out of 1079 evaluable subjects, representing 1.5% of ADA evaluable subjects) had ADA titer values greater than or equal to 128.

Table 39: Overall Summary of Incidence of Anti-Drug Antibodies (Anti-Risankizumab Antibodies) and Neutralizing Antibodies to Risankizumab for up to 52 Weeks Duration in Phase 2 and Phase 3 Studies in Subjects with Moderate to Severe Plaque Psoriasis

	Risankizumab 18 mg SC to 180 mg SC*	Risankizumab 150 mg SC[a]	Placebo to Risankizumab 150 mg SC[b]	Risankizumab 150 mg SC to placebo withdrawal with or without retreatment with risankizumab 150 mg SC[c]	Adalimumab to Risankizumab 150 mg SC[d,**]	Total (at least one dose of risankizumab 150 mg SC)	Total (at least one dose of risankizumab at any dose)
	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 2 and 3
Evaluable subjects; N	124	1079	290	224	90	1683	1807
ADA incidence (treatment emergent); N (%)	18 (14.5%)	263 (24%)	47 (16%)	65 (29%)	25 (28%)	400 (24%)	418 (23%)
NAb incidence (treatment emergent); N (%)	4 (3.2%)	150 (14%)	29 (10%)	39 (17%)	13 (14%)	231(14%)	235 (13%)

NAb = neutralizing antibody; SC = subcutaneous

* Week 0 to Week 48 only.

** Week 0 to Week 44 only.

a. Subjects who received risankizumab from Week 0, i.e., 150 mg SC at Week 0, Week 4 and q12w thereafter.

b. Subjects received placebo at Week 0 and Week 4, and switched to risankizumab at Week 16.

c. Subjects received risankizumab dose at Week 0, Week 4, and Week 16 and were withdrawn from risankizumab therapy afterwards (subjects re-randomized to placebo in Part B of the Study M15-992 (1311.4) and received re-treatment with risankizumab, if relapsed during placebo withdrawal.

d. Subjects received adalimumab from Week 0 to 15, and switched to risankizumab at Week 16.

Evaluable subjects: subjects with at least one reportable assessment at any time in the study post baseline.

NAb was assessed only when the ADA assessment was confirmed positive.

Based on the population pharmacokinetic analyses, ADA to risankizumab did not have an effect on risankizumab clearance or exposure in majority of ADA-positive subjects, with exception of few subjects (28/1807; representing 1.5% of ADA-evaluable subjects) who developed ADA titer ≥ 128 titer units, in which risankizumab clearance was estimated to increase by 43% and steady-state AUCtau was estimated to decrease by 30%, on average. Presence of neutralizing antibodies (NAb) to risankizumab was not correlated with risankizumab clearance.

To assess the *effect of immunogenicity to risankizumab on efficacy*, PASI 90 and sPGA 0/1 responses were compared between ADA-positive and ADA-negative as well as NAb-positive and NAb-negative subjects using pooled data across Phase 3 studies. The Week 16 comparisons were done using placebo-controlled population and ustekinumab-controlled population from Phase 3 studies. The Week 52 comparisons were done using ustekinumab-controlled population.

Table 40: Risankizumab PASI 90 and sPGA 0/1 Responses by ADA Status at Week 16 and Week 52

Efficacy Response (NRI)	Week 16 (Placebo Controlled; N = 1000)		Week 52 (Ustekinumab Controlled; N = 598)	
	ADA positive (N = 181)	ADA negative (N = 819)	ADA positive (N = 142)	ADA negative (N = 456)
sPGA 0/1, N (%)	154 (85.1%)	695 (84.9%)	122 (85.9%)	385 (84.4%)
PASI90, N (%)	133 (73.5%)	610 (74.5%)	109 (76.8%)	377 (82.7%)

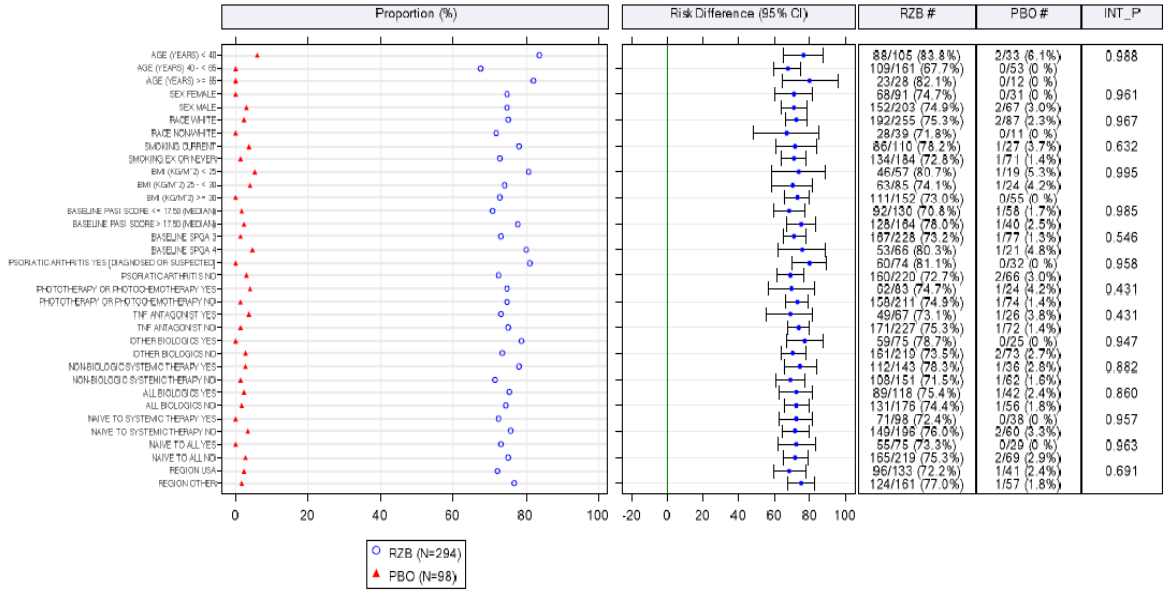
Table 41: Risankizumab PASI 90 and sPGA 0/1 Responses by NAb Status

Efficacy Response (NRI)	Week 16 (Placebo Controlled; N = 999)		Week 52 (Ustekinumab Controlled; N = 598)	
	NAb positive (N = 76)	NAb negative (N = 923)	NAb positive (N = 78)	NAb negative (N = 520)
sPGA 0/1, N (%)	64 (84.2%)	784 (84.9%)	67 (85.9%)	440 (84.6%)
PASI90, N (%)	56 (73.7%)	686 (74.3%)	59 (75.6%)	427 (82.1%)

PASI 90 and sPGA 0/1 responses at Week 16 and Week 52 were comparable between subjects who were ADA or NAb positive and those who were ADA or NAb negative. Additionally, in exposure-response analyses, the ADA and NAb status (positive or negative) were not found to be significant covariates for efficacy endpoints, PASI 75, PASI 90, PASI 100 or sPGA0/1 at Week 16 or at Week 52.

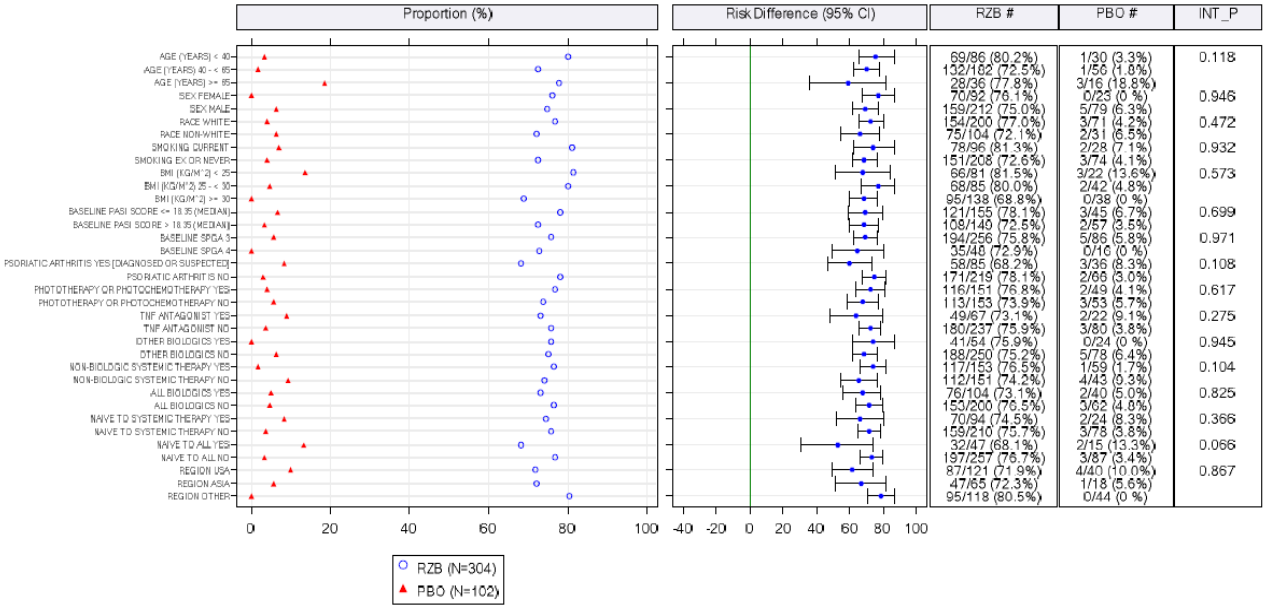
Ancillary analyses for both M15-995 and M16-008

Table 42: Proportion of Subjects With PASI 90 at Week 16, by Subgroup, NRI (ITT Population) study M15-995



BMI = body mass index; CI = confidence interval; INT_P = *P* value for treatment-subgroup interaction; ITT = Intent-to-Treat; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PASI 90 = achievement of ≥ 90% reduction from baseline PASI score; PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment; TNF = tumor necrosis factor; USA = United States of America

Table 43: Proportion of Subjects With PASI 90 at Week 16, by Subgroup, NRI (ITT Population) study M16-008



BMI = body mass index; CI = confidence interval; INT_P = *P* value for treatment-subgroup interaction; ITT = Intent-to-Treat; NRI = non responder imputation; PASI = Psoriasis Area and Severity Index; PASI 90 = ≥ 90% reduction in Psoriasis Area and Severity Index score; PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment; TNF = tumor necrosis factor; USA = United States of America

Table 44: Proportion of Subjects with sPGA Clear or Almost Clear at Week 16, by Subgroup, NRI (ITT Population) M15-995

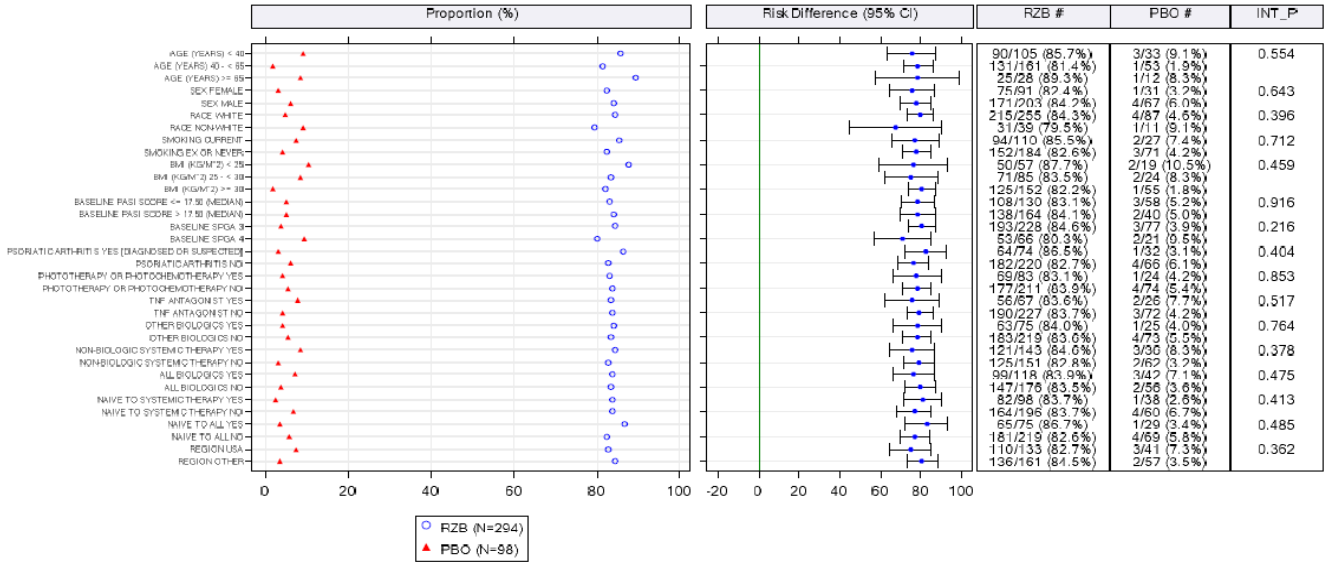
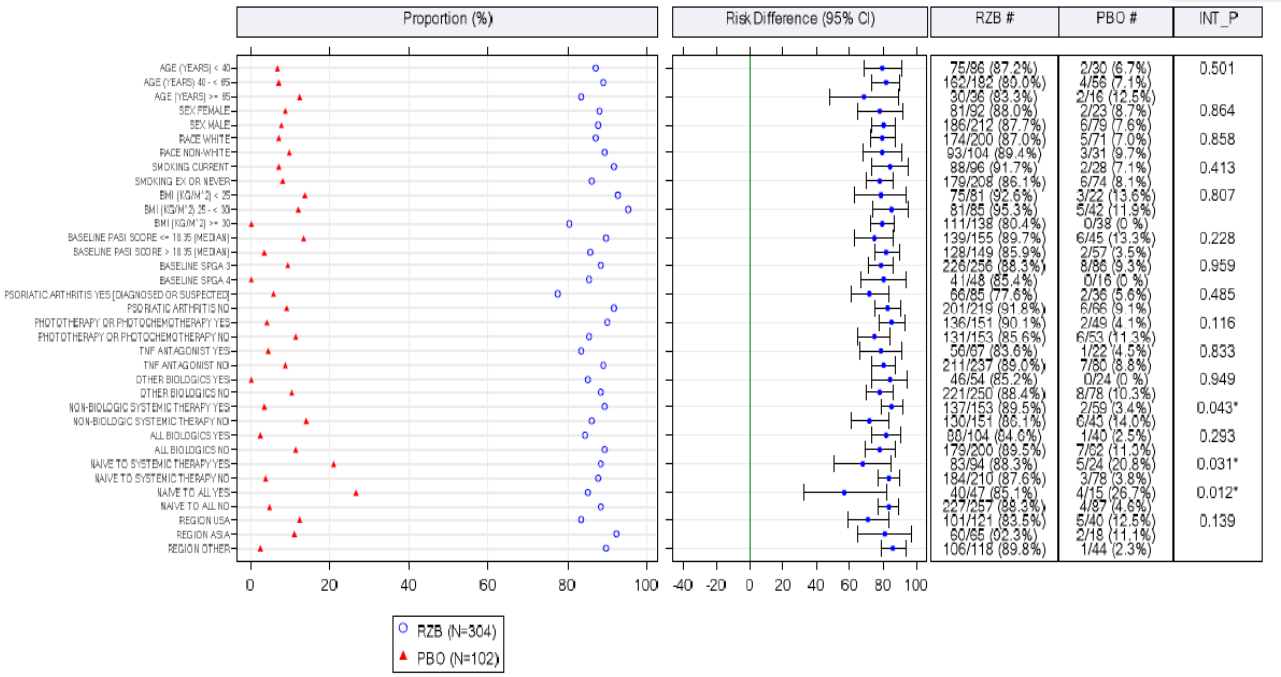


Table 45: Proportion of Subjects with sPGA Clear or Almost Clear at Week 16, by Subgroup, NRI (ITT Population) M16-008



BMI = body mass index; CI = confidence interval; INT_P = *P* value for treatment-subgroup interaction; ITT = Intent-to-Treat; NRI = non responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab; sPGA = Static Physician Global Assessment; TNF = tumor necrosis factor; USA = United States of America

\# Values for RZB and PBO are presented as n/n (%).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Trial M15-995

Title: BI 655066/ABBV-066 (Risankizumab) versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis-2			
Study identifier	M15-995		
Design	Multi-center, multi-national, randomized, 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.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks To week 40 To week 52
Hypothesis	Superiority to placebo and superiority to Ustekinumab		
Treatments groups	Placebo		Placebo for both agents s.c., 16 weeks, N=98 All patients switched to risankizumab after 16 week.
	Risankizumab 150mg 0, 4 12 weeks then every 12 weeks		52 weeks treatment , 294 randomised
	Ustekinumab		52 weeks treatment, 99 randomised
Endpoints and definitions	Co primary endpoints	PASI 90 and s PGA 0/1 at Week 16	Proportion of subjects who achieved s PGA 0/1 and Proportion of subjects who achieved PASI 90 response at Week 16 (Risankizumab vs. Placebo)
	Major Secondary endpoints. (combined)	sPGA clear wk 16	Proportion of subjects who achieved an s PGA score of 0 at 16 weeks (vs placebo and vs Ust)
		PASI 100 at wk 16	Proportion of subjects who achieved a PASI score of 100 at 16 weeks (vs placebo and vs Ust)
		DLQI 0 or 1 wk 16	Proportion of subjects who achieved DLQI score of 0 or 1 at 16 weeks (vs placebo and vs Ust)
		PSS wk 16	Change from baseline in PSSD symptom score at Week 16 (vs placebo and vs Ust)
		PASI 90 wk 52	Proportion of subjects who achieved a PASI score of 90 (vs Ust) at week 52
		PASI 100 wk 52	Proportion of subjects who achieved a PASI score of 100 (vs Ust) at week 52
		S PGA clear wk 52	Proportion of subjects who achieved an s PGA score of 0 at 52 weeks (vs Ust)
Database lock	Not stated requested		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	placebo	Risankizumab	Ustekinumab
	Number of subject	98	294	99

	s PGA score 0/1 N (%) wk 16	5/98 (5.1%)	246/294 (83.7%)	61/99 (61.6%)
	PASI 90 responders N(%) wk 16	2/98 (2.0%)	220/294 (74.8%)	47/99 (47.5%)
	PASI 100 at wk 16	2/98 (2.0)	149/294 (50.7)	24/99 (24.2)
	sPGA of 0 wk 16	3/98 (3.1)	150/294 (51.0)	25/99 (25.3)
	DLQI 0 or 1 wk 16	4/98 (4.1)	196/294 (66.7)	46/99 (46.5)
	PSS wk 16	-0.027 (0.3316)	–6.402(0.2193)	-5.560 (0.3340)
	PASI 90 wk 52	N/A	237/294 (80.6%)	50/99 (50.5%)
	PASI 100 wk 52	N/A	175/294 (59.5%)	30/99 (30.3%)
	S PGA clear wk 52	N/A	175/294 (59.53%)	30/99 (30.3)
Effect estimate per comparison	Co Primary endpoints	Comparison groups	Risankizumab vs placebo	
		P-value	P< 0.001	
	Secondary endpoints (all)	Comparison groups	Risankizumab vs placebo at 16 weeks	
		P-value	P< 0.001	
	Secondary endpoints (all)	Comparison groups	Risankizumab vs Ustekinumab	
		P-value	P< 0.001	
Notes	All secondary endpoints were highly statistically significant in favour of risankizumab treatment p < 0.001			

Trial M16-008

Title: BI 655066/ABBV-066 (Risankizumab) versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis-2		
Study identifier	M16-008	
Design	Multi-center, multi-national, randomized, 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.	
	Duration of main phase:	16 weeks
	Duration of Run-in phase:	To week 40
	Duration of Extension phase:	To week 52
Hypothesis	Superiority to placebo and superiority to Ustekinumab	
Treatments groups	Placebo	Placebo for both agents s.c., 16 weeks, N=102 All patients switched to risankizumab after 16 week.
	Risankizumab 150mg 0, 4 12 weeks then every 12 weeks	52 weeks treatment , 304 randomised
	Ustekinumab	52 weeks treatment, 100 randomised

Endpoints and definitions	Co primary endpoints	PASI 90 and s PGA 0/1 at Week 16	Proportion of subjects who achieved s PGA 0/1 and Proportion of subjects who achieved PASI 90 response at Week 16 (Risankizumab vs. Placebo)
	Major Secondary endpoints. (combined)	sPGA clear wk 16	Proportion of subjects who achieved an s PGA score of 0 at 16 weeks (vs placebo and vs Ust)
		PASI 100 at wk 16	Proportion of subjects who achieved a PASI score of 100 at 16 weeks (vs placebo and vs Ust)
		DLQI 0 or 1 wk 16	Proportion of subjects who achieved DLQI score of 0 or 1 at 16 weeks (vs placebo and vs Ust)
		PSS wk 16	Change from baseline in PSSD symptom score at Week 16 (vs placebo and vs Ust)
		PASI 90 wk 52	Proportion of subjects who achieved a PASI score of 90 (vs Ust) at week 52
		PASI 100 wk 52	Proportion of subjects who achieved a PASI score of 100 (vs Ust) at week 52
		S PGA clear wk 52	Proportion of subjects who achieved an s PGA score of 0 at 52 weeks (vs Ust)
Database lock	Not stated requested		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	placebo	Risankizumab	Ustekinumab
	Number of subject	102	304	102
	s PGA score 0/1 N (%) wk 16	8/102 (7.8%)	267/304 (87.8%)	63/100 (63.0)
	PASI 90 responders N(%) wk 16	5/102 (4.9%)	229/304(75.3%)	42/100 (42.0)
	PASI 100 at wk 16	0/102 (0)	109/304 (35.9)	12/100 (12.0)
	sPGA of 0 wk 16	2/102 (2.0)	112/304 (36.8)	14/100 (14.0)
	DLQI 0 or 1 wk 16	8/102 (7.8)	200/304 (65.8)	43/100 (43.0)

	PSS wk 16	0.157 (0.3476)	–5.608 (0.2254)	-4.436 (0.3463)
	PASI 90 wk 52	N/A	249/304 (81.9)	44/100 (44.0)
	PASI 100 wk 52	N/A	171/304 (56.3)	21/100 (21.0)
	S PGA clear wk 52	N/A	175/304 (57.6)	21/100 (21.0)

Effect estimate per comparison	Co Primary endpoints	Comparison groups	Risankizumab vs placebo
		P-value	P< 0.001
	Secondary endpoints (all)	Comparison groups	Risankizumab vs placebo at 16 weeks
		P-value	P< 0.001
	Secondary endpoints (all)	Comparison groups	Risankizumab vs Ustekinumab
		P-value	P< 0.001
Notes	All secondary endpoints were highly statistically significant in favour of risankizumab treatment p < 0.001		

Study IMMvent (M16-010)

Title: BI 655066/ABBV-066 (risankizumab) Versus Adalimumab in a Randomized, Double Blind, Parallel Group Trial in Moderate to Severe Plaque Psoriasis to Assess Safety and Efficacy After 16 Weeks of Treatment and After Incomplete Adalimumab Treatment Response (IMMvent)		
Study identifier	**M16-010**	
Design	Multi-national, multicentre, randomized, double-blind, double-dummy, active controlled, parallel-design study compared risankizumab with adalimumab. This study is designed to show a benefit of risankizumab over adalimumab in terms of PASI 90 response and sPGA scores of clear or almost clear at Week 16	
	Duration of main phase: Duration of Extension phase:	16 weeks To week 44
Hypothesis	Superiority to Adalimumab At week 16 Patients who did not response to Adalimumab PASI < 50 were switched to Risankizumab. Patients who achieved PASI < 50 but < 90 were re randomized to Risankizumab or continue with Adalimumab. The study also examined whether patients who did not achieve a clinical response to Adalimumab would benefit from Risankizumab	

Treatments groups	Risankizumab 150mg 0, 4 12 weeks then every 12 weeks		44 weeks treatment, 301 randomised at baseline. 53 patients re randomised from Adalimumab at wk 16.
	Adalimumab 80mg at randomization then 40mgs at wks 1, then every 2 weeks until wk 15		44 weeks treatment, 304 randomised at baseline 56 were re randomized at wk 16.
Endpoints and definitions	Co primary endpoints	PASI 90 and s PGA 0/1 at Week 16	Proportion of subjects who achieved s PGA 0/1 and Proportion of subjects who achieved PASI 90 response at Week 16 (Risankizumab vs. Placebo)
	Major Secondary endpoints.	PASI 75 at wk 16	Proportion of randomized subjects who achieved a PASI 75 at week 16-
		PASI 100 wk 16	Proportion of subjects who achieved a PASI score of 100 at week 16
		PASI 90 at wk 44	Proportion of re randomized subjects at week 16 who achieved a PASI score of 90 at week 44
		s PGA 0/1 wk 44	Proportion of re randomized subjects who achieved an s PGA response of clear or almost clear at week 44.
		s PGA 0 wk 44	Proportion of re randomized subjects who achieved an s PGA clear response at week 44.
		DLQI 0 or 1 wk 16	Change from baseline in Dermatology Life Quality Index (DLQI) lsmean
Database lock	Not stated requested		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group		Risankizumab	Adalimumab
	Number of subject		301	304
	s PGA score 0/1 N (%) wk 16		252/301 (83.7%)	183/304(60.2%)
	PASI 90 responders N(%) wk 16 PASI 90 responders N(%) wk 44		218/301(72.4%) 35/53 (66.0%)	144/304(47.4%) 12/56 (21.4%)
	PASI 75 at wk 16 PASI 100 at wk 16		273/301 (90.7%) 120/301 (39.9%)	218/304 (71.7%) 70/304 (23.0%)
	PASI 90 at wk 44 PASI 100 at wk 44 s PGA 0/1 wk 44 s PGA 0 wk 44 DLQI 0 or 1 wk 16		35/53 (66.0%) 21/52 (39.6%) 39/53 (73.6%) 21/53(39.6%) -11.5	12/56 (21.4%) 4/56 (7.1%) 19/56 (33.9%) 4/56 (7.1%) -9.7
Effect estimate per comparison	Co Primary endpoints at 16 and 44 weeks	Comparison groups	Risankizumab vs Adalimumab	
		P-value	P< 0.001	

	Secondary endpoints (all) at 16 weeks and 44 weeks	Comparison groups	Risankizumab vs Adalimumab
		P-value	P< 0.001
Notes	All secondary endpoints were highly statistically significant in favour of risankizumab treatment p < 0.001		

M15-992

Title: BI 655066 [risankizumab] Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment			
Study identifier	**M15-992**		
Design	This Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study which compares risankizumab with placebo in the treatment of moderate to severe chronic plaque psoriasis. It included an 88-week treatment period and a 16-week follow-up period.		
	Part A (double-blind period) Duration of main phase (A1) Phase A2 **Part B** (Randomized Withdrawal and Re Treatment) period Follow up		16 weeks week 16 to week 28 week 28 to week 88 week 88 to week 104
Hypothesis	Superiority to placebo		
Treatments groups	**Part A** Placebo		Placebo 28 weeks, N =100
	Part A Risankizumab 150mg 0, 4 12 weeks then every 12 weeks		28 weeks , N= 407 randomised At week 28 patients assessed for response Subjects who met the protocol-defined response criterion (Static Physician Global Assessment [sPGA] clear or almost clear) were re-randomized in a ratio of 1:2 to double-blind risankizumab or placebo (part B study)
	Part B (re-randomized to placebo)		Placebo week 28 to week 88, N =225
	Part B (re-randomized to Risankizumab) 150mg every 12 weeks		Placebo week 28 to week 88, N =111
Endpoints and definitions	**Part A** Co primary endpoints	PASI 90 and s PGA 0/1 at Week 16	Proportion of subjects who achieved s PGA 0/1 and Proportion of subjects who achieved PASI 90 response at Week 16 (Risankizumab vs. Placebo)

	Part A Major Secondary endpoints.	PASI 75 at wk 16	Proportion of subjects who achieved a PASI score of 100 at 16 weeks (vs placebo)
		PASI 100 at wk 16	Proportion of subjects who achieved a PASI score of 100 at 16 weeks (vs placebo)
		sPGA clear at wk 16	Proportion of subjects who achieved an sPGA score of 0 at 16 weeks (vs placebo)
		DLQI 0 or 1 wk 16	Proportion of subjects who achieved DLQI score of 0 or 1 at 16 weeks (vs placebo)
	Part B	sPGA 0/1 at Week 52	Proportion of subjects who achieved sPGA 0/1 and at Week 52 among subject re-randomized at week 28 (Risankizumab vs. Placebo)
Database lock	The interim report provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
	Part A		
Descriptive statistics and estimate variability	Treatment group	placebo	Risankizumab
	Number of subject	100	407
	s PGA score 0/1 N (%) w16	7/100(7%)	340/407(83%)
	PASI 90 responders N(%) w16	2/100(2%)	298/407(73%)
	PASI 75 at wk 16	8/100 (8%)	361/407(89%)
	PASI 100 at wk 16	1/100 (1%)	192/407(47%)
	sPGA clear at wk 16	1/100 (1%)	189/407(46%)
	DLQI 0 or 1 wk 16	3/100 (3%)	266/407(65%)
	Part B (after re-randomization)		
	Treatment group	Placebo	Risankizumab
	Number of subject	225	111
	s PGA score 0/1 N (%) wk 52	138/225(61%)	97/111(87%)
Effect estimate per comparison	Co Primary endpoints for part A	Comparison groups	Risankizumab vs placebo
		P-value	P< 0.001
	Secondary endpoints	Comparison groups	Risankizumab vs placebo at 16 weeks

	Ranked	P-value	P< 0.001
	Primary endpoint for part B	Comparison groups	Risankizumab vs vs placebo
		P-value	P< 0.001
Notes			

2.5.3. Discussion on clinical efficacy

Discussion on clinical efficacy

Introduction

The clinical development plan follows a standard clinical package for a new product for the treatment of plaque psoriasis and is in line with in line with scientific advice received from the CHMP and the Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr).

The Applicant has conducted an extensive clinical development program in support of the marketing authorisation in moderate to severe plaque psoriasis. Risankizumab has been investigated in phase 2 study (Study 1311.2) and three pivotal studies (studies M15-995, M16-008 and M16-010). In addition study M15-992 after the initial 28 weeks double-blind period investigated the effect of withdrawal and re-treatment with risankizumab. Maintenance of efficacy was further investigated in the open-label extension study.

Design and conduct of clinical studies

The study designs are agreed with respect to study design, duration, patient population, clinical endpoints and chosen active comparators.

The co primary endpoints of PASI 90 and s PGA 0/1 are agreed as they are clinically relevant and in line with other centralised authorisations. Recent authorised products have demonstrated excellent results in terms of response therefore it is justified that higher PASI responses are measured (PASI 90 and 100), however, for comparative purposes, PASI 50 and PASI 75 are also useful parameters.

The s PGA is considered a valid measure of psoriasis disease severity and has a more stringent definition for a score of 1 (“almost clear”) and 0 (Clear).

PASI 90 was considered by CHMP to represent a clinically more relevant improvement over PASI 75, and the sPGA was considered to be a validated, standardised, global score that is recommended to be used in conjunction with PASI. The CHMP advised that a 6-point PGA scale (severe, moderate to severe, moderate, mild, almost clear, clear) should preferably be used in account of comparability to recent studies in psoriasis. A 5-point scale was ultimately employed in the risankizumab studies. The 5-point sPGA scale used is similar to the scales used in recently approved drugs for psoriasis, including Tremfya and Cosentyx. The only real difference is an additional 'very severe' level at the 'high' end of the 6-point scale compared with the highest level of 'severe' for the 5-point scale. This difference is expected to have minimal impact on the patient population included in the clinical trials.

Longer duration of effect at 44 and 52 weeks were measured and also quality of life measurements for patients in the trial. The applicant also developed and validated a patient reported outcome instrument, psoriasis severity

The pivotal studies were multicentre and all had a randomized double-blind placebo- and active-controlled parallel group study design. The co primary endpoints were assessed at week 16 for efficacy.

Maintenance of effect was examined up to 52 weeks in studies M15-995, M16-008 or up to 44 weeks in study M16-010. In the M15-992 study it is planned to investigate the efficacy up to 88 weeks however in the interim report the data upto 52 weeks were provided. The long term extension study is ongoing with the plan to monitor efficacy up to week 156 and included in the RMP as category 3 study.

The included patient population corresponds to the definition of moderate to severe chronic plaque psoriasis in terms of disease severity (PASI score and body surface area) and were in need of systemic therapy.

Patients enrolled had heterogeneous treatment history and varied from treatment naïve to prior failure to other biological therapies. Patients entering the trial were stratified on anti TNF failure and body weight (> or < 100kgs).

Ustekinumab was chosen as an active comparator in studies M15-995, M16-008 and in study M16-010 Adalimumab was the active comparator. Both are considered as acceptable as active comparators as both are prescribed in practise and have different pathways.

Furthermore patients who were not adequately controlled on either of these active comparators were switched to Risankizumab to demonstrate whether additional benefit was observed.

The efficacy results using Ustekinumab as an active comparator were similar to the original studies and therefore added to internal validity.

As both studies M15-995, M16-008 were identical and the findings were consistent and therefore quite robust.

The applicant has developed and validated a patient reported outcome instrument, psoriasis symptom scale (PSS). PSS is a patient-reported outcome measure developed by the Applicant. This was aimed to detect signs and symptoms experienced by a patient on a daily basis. During validation high internal consistency- and test-retest-reliability were demonstrated.

Study M15-992 (1311.4) was placebo controlled randomized double-blind study in patients with moderate to severe chronic plaque psoriasis evaluating the efficacy and safety with randomized withdrawal and re-treatment. In part A of this study subjects were randomized to one of 2 treatment arms: risankizumab (arm A1) or placebo (arm A2). At the Week 28 visit, all subjects were assessed for response. Subjects in Arm 1 (originally randomized to risankizumab) who met the protocol-defined response criterion (Static Physician Global Assessment [sPGA] clear or almost clear) were re-randomized in a ratio of 1:2 to double-blind risankizumab or placebo (part B of the study). Beginning at Week 32, all subjects in who received blinded study drug or placebo at Week 28 and had sPGA ≥ 3 (relapse) were switched to open-label risankizumab.

The study design was in line with the current EMA guidance on clinical investigation of products for the treatment of psoriasis. The subsequent withdrawal and re-treatment phase allows examining the duration of response, rebound and time to relapse.

The clinical studies were adequately powered to detect clinically meaningful differences between groups on the primary endpoints. The statistical methods used to analyse the primary and secondary endpoints were appropriate with adequate control of the study-wise type I error. The methods for handling missing data were appropriate given the context of the disease under study, the limited proportion of missing data observed in each study and the magnitude of the observed treatment effects.

Efficacy data and additional analyses

Dose response studies

The recommended dose and dosing regimen used in the Phase 3 studies were selected based on safety, efficacy and pharmacokinetic data from the Phase 1 (Study 1311.1) and Phase 2 (Study 1311.2) studies in adult patients with plaque psoriasis, formulation considerations, patient acceptability considerations, as well as exposure-response analyses.

An indirect-response PK-PD model was developed using PK and time course of PASI score data from Studies 1311.1 and 1311.2.

The PK-PD modelling is in agreement with the clinical data where modelling indicates the 150 mg SC dose provides efficacy at the plateau of exposure-response relationship for efficacy. Doses above 150 mg were predicted to result in minimal improvements (< 5%) in PASI 90 or PASI 100 responses. The modelling also predicted that inclusion of the additional dose at week 4 would provide higher PASI 90 response rates at earlier time points (e.g., Week 12 and Week 16) compared with regimens without this additional dose.

In phase I first-in-human single dose study (study 1311.1), at doses of 0.25 mg/kg (~19 mg for 75 kg patient), 1, 3, and 5 mg/kg (~375 mg for 75 kg patient) by IV or SC administration, all active dose groups showed improvement in mean PASI scores at 24 week follow-up with doses > 1 mg/kg showing near maximal PASI reduction.

For the phase II dose ranging study (Study 1311.2) 3 doses were selected e.g mg 18 SC single dose at Week 0, and 90 and 180 mg SC multiple doses at Weeks 0, 4, and 16. In this study the dose-response was evaluated on outcomes such as PASI responder rates at 90% at week 12 (primary endpoint), 75, 50 and 100% levels, PGA scores and DLQ index. This is in line with the EMA psoriasis Guideline that recommends using a global psoriasis endpoint along with PASI response.

The selected study population was compatible with the patient population in the pivotal studies and representative of the target population.

In this study, overall, best results were obtained for 90mg and 180 mg dose as compared to 18 mg for which a significant difference as compared to Stelara was not seen for most endpoints.

For doses 90 mg and 180 mg dose mixed efficacy results were reported. Both 90mg and 180 mg doses were superior as compared to Stelara for PASI 90 at Week 12 but not for PASI 90 at Week 24, as at this time point only 180 mg dose was better to Stelara. Also at Week 12 the 90mg dose was superior to Stelara for PASI 75.

In line with the SmPC the recommended dose is 150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

The 150 mg dose and dosing regimens (e.g. Week 0, Week 4, and every 12 weeks thereafter) was selected based on the results of the Population Pharmacokinetic and Exposure-Response Analyses of Risankizumab from Phase 1 and 2 Studies in Subjects with Psoriasis which included data from phase I (study 1311.1) and phase II study (study 1311.2). It can be noted that the proposed dosage regimen is the same as the posology approved for Stelara (ustekinumab), with the same target (IL-23) and with a similar half-life as risankizumab (approximately 3 weeks).

Under the proposed regimen, doses of 150 mg are predicted to result in near maximal PASI 90 and PASI 100 rates; additional increases in dose of risankizumab up to two-fold (300 mg) are predicted to result in no more than a 5% increase in PASI 90 response rates.

In addition alternative dosing regimens were investigated in this PK/PD analysis. Based on PK-PD considerations alone, the 0, week4 q8 regime offers only minimal advantages over q12 while for q16 decreased efficacy was observed. It is noted that the predicated time to the first loss of PASI 90 response for doses >90 mg was long e.g. > 300 days. It is known that patients with psoriasis tend to be overweight or obese. Some of the biological products approved for use in psoriasis have a weight-based posology

(Remicade, Stelara), while others don´t (e.g. Humira, Enbrel and Cosentyx). For Stelara (ustekinumab), a cut-off is applied, with patients weighing >100 kg receiving the double dose. The applicant claims that the weight-based posology is not required as the predicted median response rates for PASI 90 and PASI 100 would only differ by about 5% for a body weight of 60 kg vs. 120 kg based on the PASI PK-PD model.

Phase 3 studies

A total of 2109 subjects were randomized in the Phase 3 studies. Of those subjects, 1306 were randomized to risankizumab. An additional 375 subjects switched to risankizumab in later parts of the pivotal studies, and 348 subjects switched to risankizumab in the open-label extension Study M15-997.

Studies M15-995, M16-008

For the identical phase 3 studies M15-995, M16-008 the co primary endpoints were statistically significantly higher for Risankizumab treatment compared to both placebo and Ustekinumab.

Starting at Week 12, statistically significant differences in favour of risankizumab for proportions of subjects who achieved all PASI 75/90/100, as well as sPGA of clear/clear or almost clear were observed.

At week 16 PASI 90 responses were 74.8% to 75.3 % with Risankizumab treatment compared to placebo responses of 2-4.9% and were statistically significant (p< 0.001).

S PGA responses at Week 16, ranged from 83.7% to 87.8% compared with placebo (ranged 5.1 to 7.8%) and were also highly statistically significant (p< 0.001).

Both showed similar positive results. The applicant also conducted several sensitivity analyses which supported the primary ITT analyses.

Ranked secondary endpoints which involved comparisons to placebo and active comparator Ustekinumab were all statistically in favour of Risankizumab treatment.

These endpoints included higher response rates such as s PGA clear at 16 weeks (ranged 36.8- 51 % P < 0.001) and PASI 100 (ranged from 35.9- 50.7% P < 0.001) when compared to placebo.

Higher responses were also seen in compared to Ustekinumab at week 16 sPGA 0/1 was between 22.1%-24.8% p < 0.001 and for PASI 90 at week 16 were 22.8 to 25.7% higher both p < 0.001.

The co primary endpoints at week 16 were maintained until week 52 and achieved better results compared to Ustekinumab s PGA was 17.2 to 17.5% higher P < 0.001 and for PASI 90 at week 52 30.15 to 37.9 % P < 0.001 in favour of Risankizumab.

It was also noted that statistically significant improvement in more difficult to treat areas of psoriasis were noted such as Palmoplantar Psoriasis (PPASI), Nail psoriasis (NAPSI) and scalp psoriasis at 16 and at 52 weeks with Risankizumab treatment. This information will be added to the SPC in section 5.1.

The applicant is asked to further discuss the NAPSI, PSSI, PPASI and PSS scores at baseline and the cut off values for mild moderate and severe categories.

Improvements were observed in psoriasis involving the scalp, the nails, and the palms and soles at week 16 and week 52 in subjects treated with risankizumab as mentioned below.

Table 46: Mean changes from baseline in NAPSI, PPASI, and PSSI

	ULTIMMA-1		ULTIMMA-2		IMMHANCE	
	Risankizumab	**Placebo**	**Risankizumab**	**Placebo**	**Risankizumab**	**Placebo**
NAPSI: Change at Week 16 (SE)	N=178; -9.0 (1.17)	N=56; 2.1 (1.86) ***	N=177; -7.5 (1.03)	N=49; 3.0 (1.76) ***	N=235; -7.5 (0.89)	N=58; 2.5 (1.70) ***
PPASI:	N=95;	N=34;	N=86;	N=23;	N=113;	N=26;

Change at Week 16 (SE)	-5.93 (0.324)	-3.17 (0.445) ***	-7.24 (0.558)	-3.74 (1.025) **	-7.39 (0.654)	-0.27 (1.339) ***
PSSI: Change at Week 16 (SE)	N=267; -17.6 (0.47)	N=92; -2.9 (0.69) ***	N=252; -18.4 (0.52)	N=83; -4.6 (0.82) ***	N=357; -20.1 (0.40)	N=88; -5.5 (0.77) ***
NAPSI: Change at Week 52 (SE)	N=178; -15.7 (0.94)	-	N=183; -16.7 (0.85)	-	-	-
PPASI: Change at Week 52 (SE)	N=95; -6.16 (0.296)	-	N=89; -8.35 (0.274)	-	-	-
PSSI: Change at Week 52 (SE)	N=269; -17.9 (0.34)	-	N=259; -18.8 (0.24)	-	-	-
Nail Psoriasis Severity Index (NAPSI), Palmoplantar Psoriasis Severity Index (PPASI), Psoriasis Scalp Severity Index (PSSI), and Standard Error (SE) ** P < 0.01 comparing to risankizumab *** P < 0.001 comparing to risankizumab						

Also the improvements in psoriasis correlated with improvements in quality of life for patients. Statistically significant improvement in DLQI score and PSS at 16 weeks were achieved with Risankizumab treatment. Additional endpoints included HAQ DI, HADS, and DLQI score form baseline, at later time points week 52 were also measured. As some were comparable or better than Ustekinumab not all were statistically better further information is requested on their clinical meaning.

The Company developed a PSS is a 4-item patient-reported outcome (PRO) instrument designed for this program that assesses the severity of psoriasis symptoms in patients with moderate to severe psoriasis. The PSS was developed based on published evidence supporting the development of 2 similar, proprietary PRO instruments: the Psoriasis Symptom Inventory and the Psoriasis.

Symptom Diary. The PSS items assess severity of pain, itching, redness, and burning during the past 24 hours. These measures were developed in accordance with FDA PRO Guidance and have demonstrated its evidence of reliability, validity, and ability to detect change.

The Applicant stated that responder definition (clinically meaningful changes) in PSS symptom and signs summary score was estimated by using both an anchor and distribution-based approach a change in s PGA score and a PASI improvement at week 16 were considered as reasonable anchors to establish response

The psychometric analysis findings support the validity and responsiveness of the PSS. Additionally, cumulative distribution functions indicate that across the full distribution of changes in PSS total score, risankizumab is associated with greater percentages of patients with improvement in psoriasis-related symptoms versus placebo or ustekinumab.

The Applicant also conducted extensive subgroup analyses in the population for each co primary endpoint and showed clear separation from placebo in each group.

In the phase 3 studies, all protocol amendments occurred before database lock. Protocol violations discussed by the Applicant in the CSRs could not influence the integrity of studies.

However a GCP issue was noted and occurred in study M15-995. One Site was closed during study conduct due to failure of the site to adhere to the signed agreement, the study protocol and procedures,

and GCP. The 11 subjects enrolled at this site were excluded from the efficacy and safety analyses as planned in the SAP.

A sensitivity analysis of the co-primary endpoints at Week 16 including these subjects was generated, however did not affect the results.

Study M16-010

This was a Phase 3, multi-national, multicentre, randomized, double-blind, double-dummy, active controlled, parallel-design study compared risankizumab (RZB) with adalimumab.

This study is designed to show a benefit of risankizumab over adalimumab in terms of PASI 90 response and sPGA scores of clear or almost clear at Week 16, duration was 44 weeks and enrolled 605 patients in a 1:1 ratio.

At Week 16, patients initially on adalimumab and >PASI 50 and <PASI 90 will be re-randomised 1:1 to receive either risankizumab or adalimumab, Patients achieving < PASI 50 were switched to Risankizumab and those achieving PASI > 90 continued on Adalimumab.

The trial population and endpoints were similar to the identical phase 3 studies (M15-995 and M16-008).

Psoriasis medication history was generally balanced among inadequate adalimumab responders who were re-randomized to risankizumab compared with adalimumab. However, a notably larger proportion of subjects who were re-randomized to risankizumab (60.4%) had prior non-biologic systemic therapy compared with subjects re-randomized to adalimumab (41.1%).

The co primary endpoints were statistically significantly in favour of Risankizumab treatment at 16 weeks. PASI 90; 72.4 % compared to 47.4% and sPGA 83.7% compared to 60.2% (both p < 0.001 risankizumab and Adalimumab resp).

A statistically higher proportion of patients re randomised to Risankizumab arm after 16 weeks (patients who achieved PASI > 50 and < 90 previously treated on ADA) achieved PASI 90 or s PGA response at week 44. This was also supported by the sensitivity analyses. The response rate for PASI 90 is slightly lower 66% compared to 72.4 % initially (i.e. at 16 weeks) and also for s PGA response of 0/1 was 73.6% compared to 83.7% at week 16, however this may because the population could be more difficult to treat.

Subjects who received continuous risankizumab saw persistent or increased responses until the end of the study; 157/301 (52.2%) achieved sPGA clear 159/301 (52.8%) achieved PASI 100 at Week 44. However it was not clear how the PASI 90 at week 52 and s PGA responses in patients who continued on Risankizumab throughout the study compared to the identical phase 3 studies M15-995 and M16-008.

Overall however a statistically significant better response was demonstrated compared to Adalimumab and patients who did not achieve the target response of PASI 90 or s PGA response achieved significantly better results when switched to risankizumab.

Study M15-992

There were 2 co-primary endpoints in this study e.g achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16 and achievement of an sPGA score of clear or almost clear (0 or 1) at Week 16.

The objectives of part B of the M15-992 (1311.4) study was to investigate the maintenance of response following drug withdrawal and to assess response after retreatment. Cases of relapse and the potential cases of rebound effect were also planned to be captured.

The maintenance of effect was measured by the achievement of an sPGA of clear or almost clear (0 or 1) at Week 52 for subjects who were re-randomization to either risankizumab or placebo at week 28. This

was the primary endpoint for Part B of this study. In this analysis subjects who discontinued due to AE of "Worsening of disease under study," or received retreatment with risankizumab for relapse during Part B, were counted as nonresponders. For patients re-randomised at Week 28 time until loss of sPGA of 0 or 1 response, time until sPGA score of ≥ 3 (relapse) and the time until loss of PASI 50, PASI 75, PASI 90, and PASI 100 were also investigated.

A total of 507 subjects were randomized to part A of the study (407 patients received blinded risankizumab and 100 received placebo). 399 out of 407 patients originally assigned to the risankizumab group in part A entered part B of the study. 336 patients classified as responders were re-randomized to ether placebo (225 subjects) or risankizumab (111 subjects). 63 out of 407 subjects from the original risankizumab group were classified as non-responders.

In general demographic parameters and baseline disease characteristics were well-balanced between arms. The mean age of enrolled subjects was 49.2 years, the majority of subjects were male and only 18% of patients had normal body weight. 55% of patients received biologic therapy before enrolment (36% TNF antagonist and 41% other biologic). The majority of patients enrolled to this study had moderate psoriasis (79%) and 21% had severe psoriasis as per sPGA score. Mean PASI score was 21.17 in the placebo group and 19.9 in the risankizumab, mean BSA was 28.3% in the placebo group and 25.6% in the risankizumab group.

Baseline demographic characteristics of responders who were re-randomized and participated in part B of the study was very similar to the initial study population (part A study).

As indicated above 111 out of 336 patients did not respond to risankizumab and 63 patients from this group were included in the ITT_B_NR Population. The comparison of baseline characteristic of patients who responded to treatment (ITT_B_R Population) to those who did notrespond was further clarified upon request**.** It seems that in the group of non-responders more patients had severe psoriasis at baseline (27%) as compared to 19 % in the responders group and there were more females in this group. In addition mean weight was slightly higher at baseline in the non-responses group.

Significantly better results as compared to placebo were achieved also for The Dermatology Life Quality Index. At week 16 in the risankizumab group 65% of patients achieved DLQI 0 or 1 as compared to only 3 % of patients in the placebo group.

The proportion of re-randomized subjects who achieved sPGA of clear or almost clear at Week 52 was pre-specified as a primary endpoint for part B of the study

The primary endpoint in Part B was achieved and at day 52 statistically better results were observed in the groups of patients who were re-randomized to risankizumab as compared to those re-randomized to placebo. It needs to be highlighted that the treatment effect was much smaller (26 % difference between the treatment groups) as compared to the treatment effect recorded during the initial randomization period (A1). Such small difference between the treatment groups was due to the fact that at week 52 (24 weeks after withdrawal treatment with risankizumab) 61.3 % of patients in the placebo group had still sPGA of clear or almost clear.

The median time until loss of sPGA of 0 or 1 response in the placebo group was 218/31 weeks (25th 114 days/16 weeks, 75th 290 days/41weeks), the median time to relapse (sPGA>=3) in this group was 288 days/41 weeks. The median time until loss of PASI 90 in part B among subjects who achieved PASI 90 at week 28 was 209 days/29 weeks. The median time to loss response could not be estimated for the maintenance group e.g. patients re-randomized to risankizumab. In the phase II study (Study 1311.2) the time to the first loss of PASI90 response was longer and it was established (median) as 309 days/44 weeks (for 90 mg dose) and 345 days/49 weeks (for 180 mg dose). No cases of rebound (defined as ≥ 25% increase in PASI relative to baseline within 60 days after re-randomization) occurred in subjects who had risankizumab treatment withdrawn.

Statistically better results were observed in the risankizumab re-randomized group as compared to the placebo group for also other endpoints such as PASI 75, PASI 90 and PASI 100.

In relation to the subgroups analysis the results better than placebo were observed in the vast majority of the subgroups. No difference as comparing to placebo were observed only in the following subgroups: race non – white, BMI<25 kg and for subjects from region Asia.

40 patients who were sPGA responders at Week 28 who were re-randomized to withdrawal (placebo) in Part B and relapsed (sPGA ≥ 3), and had at least 1 dose of risankizumab re-treatment were analysed for the response. It was noted that 85% (34/40) regained sPGA of clear or almost clear at 16 week after re-treatment. On the other hand only 65.0% achieved PASI 90 at Week 16 of re-treatment which is a slightly worse result as comparing to naïve patients who received treatment with risankizumab at the beginning of the study. It is noted that the re-treated subjects received risankizumab every 12 weeks without the induction dose (e.g. dose at week 4), unless they relapsed and re-treated before Week 70 in which case they would receive the Week 4 dose after relapse.

Only 3 subjects who were re-randomized to continue risankizumab treatment relapsed and received a loading dose at least 16 weeks prior to the re-treatment data cut-off (22 September 2017); therefore, no conclusions were drawn.

63 patients did not respond to risankizumab at week 28. However it seems that some initial non-responder may respond later e.g 38.1% of these patients achieved sPGA clear or almost clear at Week 32, and 49.2% achieved sPGA clear or almost clear at Week 52.

The Applicant proposed to include the following recommendation in the SmPC which can be accepted: Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Study M15-997

Study M15-997 (1311.31) study was a multicentre, open label study to assess the safety and efficacy of Risankizumab for Maintenance in Moderate to Severe Plaque Type Psoriasis.

As indicated by the Applicant, the goal of the provided interim report was to present novel efficacy data for the subset of subjects who were switched from ustekinumab (169 subjects) or adalimumab (260 subjects) to risankizumab at entry of Study M15-997.

In general demographic parameters and baseline disease characteristics were similar to those reported for other studies. The mean age of enrolled subjects was 47.4 years, the majority of subjects were male (>70%) and less than 19% of patients had normal body weight.

The majority of patients enrolled to this study had moderate psoriasis (>80%). Mean PASI score was 19.03 for the groups of patients transferred from ustekinumab (UST_RZB group) and 19.61 for the group of patients transferred from adalimumab (ADA_RZB group), mean BSA was 22.8% in the UST_RZB group and 25.5% in the ADA_RZB group.

In general in both groups e.g patients transferred from ustekinumab and patients transferred from adalimumab the efficacy results improve with risankizumab treatment.

Among subjects who completed Studies M15-995 (1311.28) and M16-008 (1311.3) on ustekinumab and switched to risankizumab in Study M15-997, the proportions of subjects who achieved sPGA clear or almost clear, sPGA clear, PASI 90, PASI 100, and PASI 75 increased at Week 12. For example sPGA clear or almost clear increased from 58.6% at study entry to 85.2% at week 12, whereas PASI 90 increased from 47.3% to 72.8%.

Also among subjects who completed M16-010 (1311.30) study on adalimumab and were switched to risankizumab in Study M15-997, the proportions of subjects who achieved sPGA clear or almost clear, sPGA clear, PASI 90, PASI 100, and PASI 75 increased at Week 12. Among initial responders who continued with adalimumab and switched to risankizumab in M15-997, sPGA clear or almost clear increased from 78.5% to 90.6% whereas PASI 90 increased from 73.1% to 92.2%. Among subjects who were re-randomized to adalimumab and switched to risankizumab in M15-997, sPGA clear or almost clear increased from 32.7% to 70.4% whereas PASI 90 increased from 22.4% to 77.8%.The proportions of subjects who achieved sPGA clear or almost clear, sPGA clear, PASI 90, PASI 100, and PASI 75 increased in all adalimumab subgroups including adalimumab responders and non-responders. In relation to adalimumab responders very good resulted observed at the study entry were further improved with treatment with risankizumab.

Efficacy and Antibodies to Risankizumab

For subjects who received the proposed clinical regimen of risankizumab in psoriasis (150 mg at Week 0, Week 4, and q12w thereafter) in Phase 3 trials:

- The anti-drug antibody and NAb incidence (treatment emergent) to risankizumab was 19% and 8%, respectively over 16 weeks duration (based on 1288 evaluable subjects) and 24% and 14% respectively over 52 weeks duration (based on 1079 evaluable subjects).
- The median time to appearance of ADA was 16 weeks across studies.
- A total of 16 subjects (out of 1079 evaluable subjects, representing 1.5% of ADA evaluable subjects) had ADA titer values greater than or equal to 128.

ADA positivity to risankizumab could be observed already at the baseline, after placebo treatment and in subjects treated with ustekinumab or adalimumab. Some of these risankizumab naïve patients were positive for anti risankizumab neutralizing antibodies as well. Based on the population pharmacokinetic analyses, ADA to risankizumab did not have an effect on risankizumab clearance or exposure in majority of ADA-positive subjects, with exception of few subjects (28/1807; representing 1.5% of ADA-evaluable subjects) who developed ADA titer ≥ 128 titer units, in which risankizumab clearance was estimated to increase by 43% and steady-state AUCtau was estimated to decrease by 30%, on average. Presence of neutralizing antibodies (NAb) to risankizumab was not correlated with risankizumab clearance.

To assess the effect of immunogenicity to risankizumab on efficacy, PASI 90 and sPGA 0/1 responses were compared between ADA-positive and ADA-negative as well as NAb-positive and NAb-negative subjects using pooled data across Phase 3 studies. The Week 16 comparisons were done using placebo-controlled population and ustekinumab-controlled population from Phase 3 studies. The Week 52 comparisons were done using ustekinumab-controlled population. The incidence of ADA and NAb to risankizumab per visit was comparable from Week 16 onwards to week 52, indicating stable ADA incidence following longer term treatment.

PASI 90 and sPGA 0/1 responses at Week 16 and Week 52 were comparable between subjects who were ADA or NAb positive and those who were ADA or NAb negative. Additionally, in exposure-response analyses, the ADA and NAb status (positive or negative) were not found to be significant covariates for efficacy endpoints, PASI 75, PASI 90, PASI 100 or sPGA0/1 at Week 16 or at Week 52.

The applicant provided further data which showed that patients who are ADA negative or have titres < 128 have similar results, however those with ADA titres ≥ 128 (n = 6 to 7) appear to achieve a lower response. However it is acknowledged that the numbers of patients was extremely small.

2.5.4. Conclusions on clinical efficacy

The clinical development plan consists of a standard clinical package for a new product for the treatment of plaque psoriasis and is in line with the Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr). The pivotal clinical studies are standard randomised controlled trials. The studies are agreed with respect to study design, duration, patient population and clinical endpoints.

The response to the 150mg given at baseline (loading dose), 4 weeks and every 12 weeks was statistically significantly than placebo and compared to Ustekinumab as well as Adalimumab. Furthermore improved efficacy was demonstrated in patients who had an inadequate response to Adalimumab treatment for 16 weeks. The effects of implementing a loading dose at Week 4 versus dosing every 12 weeks with no loading dose were examined by comparing efficacy results from integrated results of 3 analysis populations. efficacy rates at later time points (Week 24 and later) are comparable across the risankizumab treatment groups, this is to be expected given that the loading dose impacts the early period of treatment (onset for high levels of efficacy) and that risankizumab plasma levels in the populations that did not receive a loading dose would be approaching steady state after 5 half-lives of risankizumab. The loading dose is particularly impactful at Weeks 8 and 12, the time points at which time-to-effect has been assessed.

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 randomized withdrawal and re-treatment phase of study suggest that less frequent dosing interval or dosing based on patient's response (on demand) instead of continuous administration every two weeks may be an option. It was finally agreed that the recommended dose is 150 mg (two 75 mg injections) administered by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.

As indicated above in the M15-992 study the median time until loss of sPGA of 0 or 1 response in the placebo group was 218/31 weeks (25th 114 days/16 weeks, 75th 290 days/41weeks), the median time to relapse (sPGA>=3) in this group was 288 days/41 weeks.

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.

Overall, the applicant has demonstrated clinical relevance and consistent treatment effect in moderate to severe plaque psoriasis with a comprehensive clinical dossier. Rapporteur overall therefore agrees that Risankizumab could be approvable for MAA subject to addressing the remaining list of issues.

2.6. Clinical safety

Nine integrated analysis populations characterised the safety profile of risankizumab. Three integrated analysis sets, the Primary Safety Pool, Ustekinumab Controlled and All Risankizumab-Psoriasis, were identified by the applicant as primary to characterizing 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.

As part of the responses to the day 120 list of questions the applicant produced a Safety Update Report (SUR) as an update to the CSS (Module 2, Section 2.7.4). This SUR provides approximately 7 months of additional safety data from the data cut-off for the initial submission (01 September 2017) and includes all data up to 29 March 2018 (SUR data cut-off) for both the All Risankizumab and All Risankizumab –

Psoriasis analysis datasets. The additional 237 subjects included in this SUR for the All Risankizumab – Psoriasis Analysis Set were a result of new data from Studies M15-997, M16-178, and M16-004 (1311.38). The additional exposure data is the result of subjects who initiated risankizumab since the initial submission, as well as continued follow-up data from Studies M15-992 (1311.4), M15-997, and M16-009 (1311.13).

Integrated Analysis Sets –Primary Focus of this safety review

Analysis Population	Definition	Objective
Primary Safety Pool (N = 2232; total risankizumab exposure 420.7 PYs)	Subjects randomized to multiple dose treatment: risankizumab 150 mg in Phase 3; risankizumab 90 or 180 mg in Phase 2 through Week 16	Characterize the safety of subjects with psoriasis during the 16-week double-blind periods of the Phase 2 and Phase 3 studies
Ustekinumab-Controlled Analysis Set (N = 797; risankizumab exposure 584.0 PYs)	Subjects randomized to risankizumab 150 mg or ustekinumab followed through the end of exposure during the study	Characterize the safety of risankizumab compared with ustekinumab at 52 weeks in subjects with psoriasis
All Risankizumab Psoriasis (All RZB psoriasis) Analysis Set[a] (N = 2234; total risankizumab exposure 2,166.6 PYs)	Subjects who received a dose of risankizumab followed through the end of exposure	Characterize the long-term safety of risankizumab treatment in subjects with psoriasis

PYs = patient years; RZB = risankizumab

a. In this analysis set, "All RZB" includes all subjects who received risankizumab, regardless of dose or timing. The analysis set included the Risankizumab 150 mg group, which included all subjects randomized to risankizumab in the Phase 3 pivotal studies and subjects randomized to placebo who subsequently received 150 mg RZB.

Patient exposure

Overall exposure

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 PY of exposure. A total of 1,091 subjects received risankizumab 150 mg for ≥ 1 year. Only 3 patients received risankizumab 150mg for greater than 18months.

	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 01 September 2017. Note: Exposure is calculated using 84 days past the final dose administration.

In the Safety update report, the number of subjects exposed to at least 1 dose of risankizumab (18, 75, 90,150, or 180 mg) in the psoriasis Phase 1, Phase 2, and Phase 3 studies increased to 2,471 subjects with a total of 3351.6 PY of treatment duration, representing an additional1185.0 PY of treatment compared with the duration reported in the initial submission. In total, 1671 (67.6%) subjects were exposed to risankizumab for at least 1 year, 163 (6.6%) subjects for at least 2 years, and 85 (3.4%) subjects had ≥ 3 years of risankizumab treatment duration.

Primary safety pool

The total PY of exposure in the total risankizumab group was 420.7 PY and risankizumab 150 mg group was 395.3 PY. This compares to study drug exposure of 89.9 PY, 72.3 PY, and 93.5 PY in the placebo, ustekinumab, and adalimumab groups respectively.

Ustekinumab controlled safety population

The total PY of exposure for the risankizumab group was 584.0 PY compared to 190.8 PY for the ustekinumab group.

Four studies were ongoing at the data cut-off date M15-997 (n=1392/2000); Study M16-009 (N=110) Study; M15-992 ongoing N=507/500 and Study M16-007.

Subject Disposition

In the primary safety pool there were higher study discontinuation rates for the adalimumab (4.3%) and ustekinumab (9.6%) groups compared with the risankizumab 150mg group (1.4%) and placebo group (3.7%). However, over 98% of patients treated with risankizumab 150mg completed week 16. The commonest reasons across all treatment groups for discontinuation were adverse events, withdrawal by subject, loss to follow up and 'other' reasons. High study completions rates (95%) were maintained over 52 weeks for the ustekinumab controlled analysis group. For the All Risankizumab analysis. The available data reveals a similar patient disposition pattern to that observed in the randomized control studies. Of the 1590 subjects treated with risankizumab 150mg, 6.6% discontinued study drug. The commonest reason participants dropped out of the studies was due to withdrawal by subject, loss to follow up, adverse events and other causes. 1.6% of subjects treated with risankizumab 150mg withdrew due to adverse events.

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. Across analysis sets, approximately one third of participants were female, 80% were white 3%

Black or African Americans,10% of subjects were between 65 and 74 years of age and approximately 1% were 75 years of age or older. The majority of patients were TNFI naïve. The average subject was mid-forties in age and weighed approximately 90 kg. Although females, Black or African Americans and subjects over 65years were underrepresented in the study populations, however the results are not expected to be different from the studied population**.**

Adverse events

Overview of Treatment-Emergent Adverse Events

In the first 16 weeks of the Phase 2 and 3 psoriasis studies (Primary Safety Pool), the incidence rates of overall AEs were higher than placebo but lower than those seen with ustekinumab and adalimumab. The rates of AEs leading to discontinuation of study drug were low overall and occurred at a lower rate in the risankizumab 150 mg group (2.7E/100PY) compared to placebo (9.8E/100PY) ustekinumab (4.0E/100PY) and adalimumab (6.3E/100PY). At 16 weeks the exposure adjusted serious adverse event and severe adverse event rate in the primary safety pool is lower for risankizumab 150mg compared with the comparator groups (placebo, ustekinumab and adalimumab.

Table 47: Overview of Treatment-Emergent Adverse Events (Primary Safety Pool, 16 Weeks)

							Risankizumab							
	Placebo (N = 300) (PY = 92.0)		Ustekinumab (N = 239) (PY = 75.9)		Adalimumab (N = 304) (PY = 95.0)		90 mg (N = 41) (PY = 14.9)		150 mg (N = 1306) (PY = 402.2)		150 – 180 mg (N = 1348) (PY = 417.5)		Total (N = 1389) (PY = 432.4)	
	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)
Subjects with:														
Any adverse event (AE)	145 (48.3)	261 (283.7)	125 (52.3)	258 (339.9)	173 (56.9)	437 (460.0)	23 (56.1)	53 (355.7)	638 (48.9)	1279 (318.0)	658 (48.8)	1322 (316.6)	681 (49.0)	1375 (318.0)
Any serious AE	12 (4.0)	16 (17.4)	12 (5.0)	14 (18.4)	9 (3.0)	14 (14.7)	0	0	31 (2.4)	40 (9.9)	31 (2.3)	40 (9.6)	31 (2.2)	40 (9.3)
Any AE leading to discontinuation of study drug	9 (3.0)	9 (9.8)	3 (1.3)	3 (4.0)	6 (2.0)	6 (6.3)	1 (2.4)	1 (6.7)	9 (0.7)	11 (2.7)	9 (0.7)	11 (2.6)	10 (0.7)	12 (2.8)
Any severe AE[a]	10 (3.3)	14 (15.2)	11 (4.6)	14 (18.4)	10 (3.3)	15 (15.8)	1 (2.4)	1 (6.7)	29 (2.2)	36 (9.0)	30 (2.2)	37 (8.9)	31 (2.2)	38 (8.8)
Any AE that was assessed as related to study drug by the investigator	30 (10.0)	46 (50.0)	36 (15.1)	62 (81.7)	61 (20.1)	143 (150.5)	7 (17.1)	8 (53.7)	153 (11.7)	267 (66.4)	159 (11.8)	280 (67.1)	166 (12.0)	288 (66.6)
Any SAE that was assessed as related to study drug by the investigator	1 (0.3)	1 (1.1)	4 (1.7)	4 (5.3)	4 (1.3)	4 (4.2)	0	0	5 (0.4)	6 (1.5)	5 (0.4)	6 (1.4)	5 (0.4)	6 (1.4)
Any AE leading to death	0	0	0	0	2 (0.7)	3 (3.2)	0	0	1 (< 0.1)	1 (0.2)	1 (< 0.1)	1 (0.2)	1(< 0.1)	1 (0.2)
Deaths[b]	0	0	0	0	2 (0.7)	2 (2.1)	0	0	2 (0.2)	2 (0.5)	2 (0.1)	2 (0.5)	2 (0.1)	2 (0.5)

AE = adverse event; E = events; PY = patient-years; RCTC = Rheumatology Common Toxicity Criteria; SAE = serious AE

a. Severe AEs are defined as events with Grade 3 or 4 based on the RCTC for AEs.

b. Includes 1 non-treatment-emergent death in the risankizumab group.

Overall, the adverse event rate at 76 weeks decreases slightly to 245.7E/100PY. The SAE, severe adverse event rates and discontinuations due to AE rates for risankizumab 150mg either decrease or remain stable over longer term exposure.

Table 48: Overview of Treatment-Emergent Adverse Events (All Risankizumab – Psoriasis Analysis Set)

	Risankizumab 150 mg (N = 1590) PY = 1681.5		All Risankizumab (N = 2234) PY = 2179.0	
	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)
Subjects with:				
Any adverse event (AE)	1190 (74.8)	4132 (245.7)	1480 (66.2)	5143 (236.0)
Any serious AE[a]	109 (6.9)	167 (9.9)	139 (6.2)	213 (9.8)
Any AE leading to discontinuation of study drug	29 (1.8)	37 (2.2)	35 (1.6)	45 (2.1)
Any severe AE[a]	91 (5.7)	143 (8.5)	127 (5.7)	193 (8.9)
Any AE that was assessed as related to study drug by the investigator	324 (20.4)	734 (43.7)	396 (17.7)	889 (40.8)
Any SAE that was assessed as related to study drug by the investigator	16 (1.0)	22 (1.3)	23 (1.0)	33 (1.5)
Any AE leading to death	4 (0.3)	5 (0.3)	4 (0.2)	5 (0.2)
Deaths[b]	5 (0.3)	5 (0.3)	5 (0.2)	5 (0.2)

AE = adverse event; E = events; PY = patient-years; RCTC = Rheumatology Common Toxicity Criteria; SAE = serious AE

a. Severe AEs are defined as events with Grade 3 or 4 based on the RCTC for AEs.

b. Includes 1 non-treatment-emergent death.

Treatment emergent adverse events

Upper respiratory tract infections, viral upper respiratory tract infections, headache, arthralgia, and fatigue occurred 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 treatment groups in the primary safety analysis with a trend towards higher rates of AEs in the ustekinumab and adalimumab groups compared to risankizumab treated group. There is no obvious dose-related impact on event reporting rates. Injection site AEs were reported by 1.5% of the risankizumab treated population compared with 1.0% of the placebo population, 3.8% of the ustekinumab groups and 5.6% of the adalimumab reported AEs this group which suggests that the SC injection site reactions were less frequent with risankizumab compared to adalimumab and ustekinumab.

Common adverse events were predominately mild (>97%). The SOCs with the highest numbers of subjects with severe events at 16 weeks were- Infections and Infestation SOC: 6 subjects with severe infections (2 cases of cellulitis, 1 each of herpes zoster, diverticulitis, osteomyelitis, sepsis). Hepatobiliary disorders 3 subjects with severe events (cholecystitis, drug induced liver injury, liver injury). Gastrointestinal disorders SOC 2 subjects (enterovesical fistula gastric dilatation. Cardiac disorders 2 subjects with severe events (acute myocardial infarction, aortic valve disease mixed).

Most Frequent Adverse Events Reported in ≥ 1% of Total Risankizumab Subjects, by Frequency of PT 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)

After 52 weeks of exposure, the overall proportion of subjects with AEs in the risankizumab 150mg (70%) group was slightly lower than ustekinumab (79%). The most frequently reported AEs (≥ 5% of subjects) reported with risankizumab treatment were viral upper respiratory tract infection, upper respiratory tract infection,headache and arthralgia. 5.2% of risankizumab-treated subjects and 5.5% ustekinumab-treated subjects had AEs assessed as severe. The SOCs with the highest numbers of subjects with severe events were –Infections and infestations SOC seven subjects reported 8 types of events; cellulitis, pneumonia and sepsis (in 2 subjects each) pyelonephritis, osteomyelitis, herpes Zoster, gastroenteritis, diverticulitis. Cardiac disorders 6 subjects: SVT, mitral valve incompetence, coronary artery disease, Congestive cardiac failure, unstable angina, cardiac aneurysm. Gastrointestinal disorders 4 subjects: GERD, gastric dilatation, enterovesical fistula, dysphagia.

Table 49: Most Frequent Adverse Events Reported in ≥ 2% of Risankizumab Subjects, by Frequency of PT 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)

After long-term treatment with risankizumab 150 mg (up to 77 weeks [542 days]) influenza was the only new adverse event occurring in ≥ 2% of Risankizumab subjects identified compared to those observed during the first 16 weeks of treatment. In the All-risankizumab 150mg group approx. 75% of patients reported an AE compared with approx. 50% of patients treated with risankizumab 150mg up to 16 weeks which could be explained due to the longer duration of exposure. Similar to the other safety analysis sets viral URTI and URTI, arthralgia and headache were the commonest adverse events. 5.7% of subjects reported severe events. The SOCs with the highest numbers of subjects with severe events (≥ 3 subjects in the All Risankizumab group) were Cardiac disorders: 6 (0.3% subjects: coronary artery disease.), Infections and infestations SOC: sepsis in 6 (0.3%) subjects each; cellulitis 3 (0.1%), pneumonia 3 (0.1%). (See adverse events of special interest, serious adverse events and deaths).

Table 50: Most Frequent Adverse Events Reported in ≥ 2% of All Risankizumab Subjects, by Frequency of PT in Descending Order in the All Risankizumab Group (All Risankizumab – Psoriasis Analysis Set)

System Organ Class Preferred Term	Risankizumab 150 mg (N = 1590) n (%)	All Risankizumab (N = 2234) n (%)
Any adverse event	1190 (74.8)	1480 (66.2)
Viral upper respiratory tract infection	283 (17.8)	348 (15.6)
Upper respiratory tract infection	188 (11.8)	213 (9.5)
Arthralgia	86 (5.4)	109 (4.9)
Headache	75 (4.7)	101 (4.5)
Hypertension	54 (3.4)	70 (3.1)
Back pain	57 (3.6)	68 (3.0)
Diarrhoea	49 (3.1)	60 (2.7)
Influenza	46 (2.9)	56 (2.5)
Urinary tract infection	39 (2.5)	55 (2.5)
Gastroenteritis	41 (2.6)	49 (2.2)
Sinusitis	39 (2.5)	46 (2.1)
Fatigue	43 (2.7)	45 (2.0)
Cough	36 (2.3)	44 (2.0)
Bronchitis	33 (2.1)	44 (2.0)

In the SUR The frequencies of AEs overall in the All Risankizumab – Psoriasis Analysis Set increased from approximately 66% to 76%, which is attributed to the longer follow-up period. the overall TEAE exposure-adjusted incidence rate did not increase between the CSS (236.0 E 100/PYs) and the SUR (212.9 E/100 PYs).

There was a notable difference in the rate of viral upper respiratory tract infections (15.6% of subjects in the initial submission versus 1.3% in this SUR) and nasopharyngitis (1.6% of subjects in the initial submission versus 21.7% in the SUR). This was due to a change in MedDRA versions between the initial submission (20.0) and this SUR (20.1). No other substantial increases in the rates of AEs of safety interest were observed in this SUR and no new events of interest were identified.

Treatment related adverse events

Treatment-related adverse events were reported in 12% of risankizumab group at week 16 compared to 10% of placebo group, 15.1% of ustekinumab and 20.1% of the adalimumab treated population. Approx. 20% of the 52 week ustekinumab controlled risankizumab 150mg treated group compared to 26% of the ustekinumab treated population and 20% of the overall risankizumab 150mg treated population reported treatment related AEs. The treatment related adverse event profiles are similar across all three safety populations (URTI, viral URTI , headache, fatigue, injection site erythematic) with the exception of injection site erythematic which is reported in ≥ 1% Risankizumab 150 mg Subjects at 52 weeks and in the long term safety population but not at the 16 weeks primary safety analysis.

All Risankizumab – Psoriasis Analysis Set

Table 51: Most Frequent TEAEs (≥ 1% Risankizumab 150 mg Subjects) Assessed by Investigator as Being Possibly Related to Study Drug in Descending Order of Frequency of PT risankizumab Arm (All Risankizumab – Psoriasis Analysis Set)

System Organ Class Preferred Term	Risankizumab 150 mg (N = 1590) n (%)	All Risankizumab (N = 2234) n (%)
Any adverse event	324 (20.4)	396 (17.7)
Viral upper respiratory tract infection	42 (2.6)	59 (2.6)
Upper respiratory tract infection	47 (3.0)	55 (2.5)
Injection site erythema	26 (1.6)	31 (1.4)
Headache	18 (1.1)	20 (0.9)
Fatigue	19 (1.2)	19 (0.9)

In the Safety update review the AEs most frequently assessed by the investigators as having a reasonable possibility of being related to risankizumab treatment (≥ 2% subjects) were nasopharyngitis (consistent with remapping of lower level terms from the PT of viral upper respiratory tract infection to the PT of nasopharyngitis in this SUR) and upper respiratory tract infection.

Adverse events of special interest

Adverse events in seven areas of safety interest were specifically examined because of their higher prevalence in the moderate to severe psoriasis population, concerns with injected immunoglobulin products, the immunomodulatory activity of the product, or by general regulatory interest. The areas of special interest identified were : Infections (including serious infections, tuberculosis (TB), opportunistic infections, fungal infections, and herpes zoster); injection-site reactions; hepatic events; malignancies (including all possible malignancies, malignant tumours, nonmelanoma skin cancer [NMSC], and malignant tumours excluding NMSC);hypersensitivity and anaphylactic reactions; cardiovascular (CV) events (including major adverse cardiovascular events (MACE), extended MACE, and other CV events) depression and suicidal ideation and behaviour (SIB).

Infections (including serious infections, tuberculosis (TB), opportunistic infections, fungal infections, and herpes zoster)

There was a higher rate of infection for subjects treated with risankizumab compared with placebo and ustekinumab but not adalimumab through Week 16, (22.1% for 150 mg risankizumab (90.8 E/100 PY) vs. 14.7% (56.5 E/100 PY) for placebo, 24.3% (104.2 E/100 PY) for adalimumab and 20.9% for ustekinumab (87.0 E/100 PY)). After 52 weeks of exposure, 44.8% of subjects treated with risankizumab (73.9 E/100 PYs) and 52.3% of subjects treated with ustekinumab (90.1 E/100 PY) reported infection AEs (Ustekinumab- Controlled Analysis Set). Over the entire psoriasis program, 40.8% of subjects in the All Risankizumab group (All Risankizumab – Psoriasis Analysis Set) reported infection AEs (75.5 E/100 PY) compared with 50.1% of subjects (72.1 E/100 PY) in the SUR. In the primary safety pool the most frequently reported infection AEs in the risankizumab 150 mg group (≥ 1% of subjects) were viral upper respiratory tract infection, upper respiratory tract infection, urinary tract infection, and sinusitis.

The proportion of infections classified as serious infections was low across all three analysis populations. In the Primary Safety Pool 0.4% (1.7 E/100 PY) of the risankizumab group vs. 0.3%(1.1 E/100 PYs) of placebo group 0.3% (2.1 E/100 PY) of the adalimumab group and 1.7% (5.3 E/100PY) of ustekinumab group reported serious infections with most being single events without a clear pattern . Cellulitis (2 reports) was the only SAE reported more than once. In the Ustekinumab controlled 52-week study 1.3% subjects in the risankizumab group experienced a total of 11 serious infections (1.8 E/100 PY) compared to 2.0% subjects in the ustekinumab group with 4 serious infections (2.0(E/100 PY). For the All-risankizumab group, 29 (1.3%) subjects (1.7 E/100 PY) treated with risankizumab in the initial submission, reported serious infections compared with 38 (1.5%) subjects (1.4 E/100 PY) in the safety update report. Although the overall rate of serious infection is low, overall including the updated review

through 29 March 2018, 5 reports of cellulitis, 7 reports of sepsis 5 reports of pneumonia, 2 reports of osteomyelitis and 2 reports of serious herpes zoster were reported.

There was an increase in fungal infections reported in risankizumab treated patients compared to placebo and the Ustekinumab but not adalimumab at 16 weeks. Over 16 weeks 1.5% subjects in the risankizumab 150 mg group experienced fungal infections (5.2 E/100 PY) compared to 0.3% of the subjects in the placebo group (1.1 E/100PY), 0.8% subjects in the ustekinumab group (2.6 E/100 PY), and 2.0% subjects in the adalimumab group (7.4 E/100 PY). The event report rate remained stable over longer term exposure. Over 52 weeks 4.0% subjects in the risankizumab 150mg group experienced a total of 26 fungal infections (4.2 E/100 PY) compared to 1.0% subjects in the ustekinumab group (1.0 E/ 100 PY).). In the All- risankizumab group the event rate of fungal infections in the All-Risankizumab group in the initial submission was 3.9 E/100 PY for Risankizumab 150 mg patients compared with 3.2 E/100 PY in the SUR.

The commonest fungal infections reported in the risankizumab groups across all analyses included tinea cruris, tinea manum tinea pedis, body tinea, tinea versicolour, and fungal skin infection and onychomycosis. These infections were generally mild to moderate in severity responsive to treatment and did not require treatment discontinuation.

Ten cases of candidiasis were reported in the original overall safety analysis (Balanitis candida 1 case, Oral candidiasis 4 cases and oesophageal candidiasis 1 case, skin candida 1 case, vulvovaginal candidiasis 4 cases) Oral candidiasis cases and oesophageal candidiasis are captured both as fungal infections and opportunistic infections. These events did not result in discontinuation of study drug and were not identified as cases of serious, systemic fungal infections in the studies. With longer duration of treatment as assessed in the SUR, 22 cases of candida infection and oral candidiasis were reported. The exposure adjusted event rates increased slightly for oral candidiasis from 0.2E/100PY to 0.3E/100PY otherwise the events rates remained unchanged.

The overall event rate of opportunistic infections among risankizumab-treated subjects with psoriasis was 0.3 E/100 PY. This remained unchanged over the additional time period covered by the SUR. In the initial submission, there was one event of laboratory diagnosis of CMV and 5 reports of oral candidiasis and 1 report of oesophageal candidiasis.

There were six reports (0.4E/100PY) of Herpes Zoster in the 150 mg arm including 2 that were classified as serious infections. Through the SUR data cut-off date, a total of 13 subjects (0.5%) experienced 14 adverse events of Herpes Zoster. The number of reports of herpes zoster increased from 6 to 14 with inclusion of patients from the safety update. However, when adjusted for exposure the rate of infection increased from 0.3E/100PY to 0.4E/100PY. The overall rate of herpes zoster remained broadly stable. There were no new serious cases of herpes zoster in the SUR.

Regarding tuberculosis, the inclusion criteria specified that patients with active tuberculosis (TB) were excluded from the studies. Patients with latent tuberculosis could participate in the studies. All patients underwent TB Quantiferon test at screening. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent tuberculosis (TB) who were concurrently treated with risankizumab and appropriate TB prophylaxis during the studies, none developed active TB during a mean follow-up of 61 weeks on risankizumab. Ofthe 31 subjects in Study M15-992 who had latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on risankizumab.. Of note there were no cases of active TB. Eight cases of latent TB (0.4%: 0.4/100PY) were reported over up to 77 weeks exposure to risankizumab 150mg. Overall 8 subjects in the All Risankizumab group (all doses) reported latent TB but had no clinical symptoms. One additional case of latent TB was identified in the SUR. There were no cases of active TB among risankizumab treated patients or cases of reactivation of latent TB. Overall the rates of opportunistic infections (0.3E/100PY) were low.

Table 52: Summary of Serious Infections, Tuberculosis, Fungal Infections, and Opportunistic Infections, Including Herpes Zoster (All Risankizumab – Psoriasis Analysis Set)

	Risankizumab 150 mg (N = 1590) (PY = 1681.5)			All Risankizumab (N = 2234) (PY = 2179.0)		
	n (%)	E (E/100 PY)	[95% CI][b]	n (%)	E (E/100 PY)	[95% CI][b]
Serious infections[a]	22 (1.4)	27 (1.6)	[1.06, 2.34]	30 (1.3)	39 (1.8)	[1.27, 2.45]
Appendicitis	0	0		1 (< 0.1)	1 (< 0.1)	
Bronchitis	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Bursitis infective	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Cellulitis	5 (0.3)	5 (0.3)		5 (0.2)	5 (0.2)	
Cystitis	0	0		1 (< 0.1)	1 (< 0.1)	
Diverticulitis	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Erysipelas	0	0		2 (< 0.1)	2 (< 0.1)	
Gastroenteritis	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Herpes zoster	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
Influenza	0	0		1 (< 0.1)	1 (< 0.1)	
Meningitis bacterial	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Nasopharyngitis	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Osteomyelitis	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
Perineal abscess	0	0		1 (< 0.1)	1 (< 0.1)	
Perirectal abscess	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Pneumonia	3 (0.2)	3 (0.2)		4 (0.2)	4 (0.2)	
Polymyositis	0	0		1 (< 0.1)	1 (< 0.1)	
Pyelonephritis	1 (< 0.1)	1 (< 0.1)		2 (< 0.1)	2 (< 0.1)	
Sepsis	5 (0.3)	5 (0.3)		7 (0.3)	7 (0.3)	
Urinary tract infection	1 (< 0.1)	1 (< 0.1)		2 (< 0.1)	2 (< 0.1)	
Viral infection	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Tuberculosis	6 (0.4)	7 (0.4)	[0.17, 0.86]	8 (0.4)	10 (0.5)	[0.22, 0.84]
Latent tuberculosis	6 (0.4)	6 (0.4)		7 (0.3)	8 (0.4)	
Mycobacterium tuberculosis complex test positive	1 (< 0.1)	1 (< 0.1)		2 (< 0.1)	2 (< 0.1)	
Fungal infections	56 (3.5)	66 (3.9)	[3.04, 4.99]	64 (2.9)	75 (3.4)	[2.71, 4.31]
Balanitis candida	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Body tinea	5 (0.3)	9 (0.5)		7 (0.3)	11 (0.5)	
Fungal infection	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
Fungal skin infection	4 (0.3)	4 (0.2)		5 (0.2)	5 (0.2)	
Laryngitis fungal	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Oesophageal candidiasis	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Onychomycosis	6 (0.4)	6 (0.4)		6 (0.3)	6 (0.3)	
Oral candidiasis	3 (0.2)	4 (0.2)		4 (0.2)	5 (0.2)	
Skin candida	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Tinea cruris	3 (0.2)	3 (0.2)		4 (0.2)	4 (0.2)	
Tinea infection	0	0		1 (< 0.1)	1 (< 0.1)	
Tinea manuum	3 (0.2)	3 (0.2)		3 (0.1)	3 (0.1)	
Tinea pedis	18 (1.1)	19 (1.1)		19 (0.9)	20 (0.9)	
Tinea versicolour	5 (0.3)	6 (0.4)		5 (0.2)	6 (0.3)	
Vulvovaginal candidiasis	3 (0.2)	3 (0.2)		4 (0.2)	4 (0.2)	
Vulvovaginal mycotic infection	3 (0.2)	3 (0.2)		4 (0.2)	4 (0.2)	
Opportunistic infections	5 (0.3)	6 (0.4)	[0.13, 0.78]	6 (0.3)	7 (0.3)	[0.13, 0.66]
Cytomegalovirus infection	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Oesophageal candidiasis	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Oral candidiasis	3 (0.2)	4 (0.2)		4 (0.2)	5 (0.2)	
Herpes zoster	6 (0.4)	6 (0.4)	[0.13, 0.78]	7 (0.3)	7 (0.3)	[0.13, 0.66]

AE = adverse event; CI = confidence interval; CMQ = company MedDRA query; E = event; PY = patient year; SAE = serious adverse event

a. Serious infections in this table are SAEs identified from the Infections CMQ. Other categories of infections include AEs that are serious and nonserious.

b. 95% CI is for the exposure-adjusted event rate (E/100 PY).

Injection site reactions

The rates of injection site reactions were low across all safety analyses. At 16 weeks the proportion of subjects in the risankizumab 150 mg group who had injection site reaction AEs was higher than placebo (1.5% vs. 1.0%, respectively), but lower than with ustekinumab (3.8%) or adalimumab (5.6%). In the All Risankizumab Psoriasis Analysis Set 69 subjects (3.1%) reported injection site reactions compared with 84 subjects (3.4%) in the SUR. None of the injection site reactions were considered to be severe or led to study discontinuation. Injection site erythema was the commonest adverse event. Injection site reactions (injection site bruising, erythema, haematoma, haemorrhage, irritation, pain, pruritus, reaction, and swelling) are included as common side effects in section 4.8 of the SmPC.

Hepatic events

During the 16-week treatment period hepatic events were more frequent in placebo than for the risankizumab 150 mg treated group, 1.5% subjects in the risankizumab 150 mg group experienced a total of 24 hepatic AEs (6.0 E/100 PY) compared to 6 (2.0%) in the placebo group (7.6 E/100 PY). Overall (up to 77 weeks exposure) AEs were reported in 62 subjects (3.9%) (5.9/100PY) treated with risankizumab 150mg compared with 112 of subjects (4.5%) (5.4E/100PY) in the SUR. In the original CSS there were two reports of drug induced liver injury. One subject reported drug induced hepatitis and 1 subject reported laboratory hepatic injury -liver injury. Both cases were confounded by underlying medical conditions and concomitant medications. Both cases of liver injury were considered to be related to study drug by the investigator. A further case in the Phase 2 psoriatic arthritis study, Study M16-002, met the laboratory criteria for Hy's law 56 days after the last dose of study drug. This event occurred almost 2 months after receipt of study drug suggesting that treatment with risankizumab may have been unlikely to have played a role in the aetiology of this event. The investigator assessed the event as having a reasonable possibility of being related to study drug. Severe cases of raised LFTs (4 cases of raised AST, 3 cases of raised ALT and 1 case raised LFT were also reported, only one of which resulted in discontinuation of study medication. In the SUR an additional two subjects are reported as having had serious hepatic AEs. In the first case the subject reported autoimmune hepatitis approximately 1yr after starting risankizumab. The patient had a history of hypothyroidism, dyslipidaemia and coronary heart disease. Study drug was discontinued and LFTs normalised following treatment with prednisone. The event was reported as ongoing and not related to study medication. In the second case a subject with a baseline history of compensated cirrhosis (aetiology not reported underwent additional diagnostic tests for thrombocytopenia. Radio-diagnostics revealed portal hypertension and multinodular liver, and a diagnosis of compensated cirrhosis was made.

Liver function tests at the time of the diagnosis were not abnormal. Study drug was not interrupted due to this event and the event was considered ongoing as of the date of last contact. Both the Investigator and AbbVie considered the event of hepatic cirrhosis as having no reasonable possibility of being related to study drug and more likely due to the underlying cirrhosis.

Table 53:Summary of Hepatic AEs (All Risankizumab – Psoriasis)

Category Preferred Term	Risankizumab 150 mg (N = 1590) (PY = 1681.5)			All Risankizumab (N = 2234) (PY = 2179.0)		
	n (%)	E (E/100 PY)	[95% CI]	n (%)	E (E/100 PY)	[95% CI]
Hepatic events	62 (3.9)	100 (5.9)	[4.84, 7.23]	77 (3.4)	121 (5.6)	[4.61, 6.64]
ALT increased	17 (1.1)	19 (1.1)		24 (1.1)	26 (1.2)	
AST increased	15 (0.9)	17 (1.0)		19 (0.9)	21 (1.0)	
Drug-induced liver injury	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
GGT increased	22 (1.4)	23 (1.4)		26 (1.2)	27 (1.2)	
Hepatic enzyme increased	7 (0.4)	7 (0.4)		8 (0.4)	8 (0.4)	
Hepatic function abnormal	3 (0.2)	3 (0.2)		3 (0.1)	3 (0.1)	
Hepatic steatosis	8 (0.5)	8 (0.5)		9 (0.4)	9 (0.4)	
Hepatotoxicity	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Hyperbilirubinaemia	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Hypertransaminasaemia	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
International normalised ratio increased	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Liver disorder	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
LFT abnormal	0	0		1 (< 0.1)	1 (< 0.1)	
LFT increased	2 (0.1)	2 (0.1)		4 (0.2)	5 (0.2)	
Liver injury	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Ocular icterus	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Transaminases increased	8 (0.5)	11 (0.7)		8 (0.4)	11 (0.5)	
Ultrasound liver abnormal	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; e = event; GGT = gamma-glutamyl transferase; LFT = liver function tests; PY = patient years

Cardiovascular (CV) events (including major adverse cardiovascular events (MACE), extended MACE, and other CV events

The MACE analysis also included extended MACE and other CV events. There was no evidence of increased MACE events with risankizumab compared to placebo after 16 weeks of treatment. In the Primary Safety Pool, the MACE rate in the risankizumab 150 mg group was 0.2 E/100 PYs compared to 1.1 E/100 PYs in the placebo group. No MACE events were reported for adalimumab and ustekinumab in the initial 16-week analysis. The exposure adjusted event rates for extended MACE (0.5/100PY) and other CV events (0.5/100PY) for risankizumab 150mg were lower than those seen in the placebo arm (1.1/100PY and 3.3 /100/PY respectively)

Over 52 weeks two (0.3%) subjects (0.3 E/100 PY) in the risankizumab group experienced a MACE whilst none of the patient in the ustekinumab comparator group experienced a MACE.

In the overall risankizumab (all doses) analysis a total of 9 (0.4%) risankizumab-treated subjects experienced a treatment-emergent MACE (0.5 E/100 PY) of which 5 (0.2%) subjects had a nonfatal myocardial infarction, 2 (< 0.1%) subjects had a nonfatal stroke and 3 (0.1%) subjects had a CV death. Originally 4 of 5 treatment emergent deaths in patients treated with risankizumab 150mg were adjudicated as CV deaths. One event originally described as sudden cardiac death was later attributed to an opioid overdose. All three deaths occurred in patients with multiple CV disease risk factors, including hypertension, hyperlipidaemia, diabetes, and past history of coronary artery disease and/or intervention. All were considered unrelated to study drug by the investigator. All the events occurred in males ranging in age from age 32 to 60 yrs. No cardiac deaths were reported for adalimumab or ustekinumab and only one cardiac death was noted in the placebo group. (see section on deaths for further details).In the SUR,

13 subjects (0.5%;0.4E/100PY) experienced treatment emergent MACE(6 non-fatal MI,3 nonfatal stroke and 5 CV deaths (see sections on deaths).

The overall MACE event rate (0.5 E/100PY) was shown by the applicant to be in the range of MACE rates reported for ustekinumab, ixekizumab, secukinumab, brodalumab, and guselkumab at the time of their initial submissions. There was a slight trend towards increased numbers of events of extended MACE (0.8/100PY) and CV events (0.8/100PY) with exposure to risankizumab 150mg over the longer term. In the SUR, which included safety data up to March 2018 the numbers of events of extended MACE and CV events were 0.6E/100PY and 0.4E/100PY respectively. Although risankizumab did not appear to have any clinically significant effects on the cardiovascular functions (blood pressure, heart rate, or QT-interval) in the majority of the patients, temporal blood pressure excursions were experienced by 5.5% of the risankizumab patients through Week 52. This proportion showed slight increase up to 6.8% in the SUR. (For further details see Laboratory findings-vital signs subheading of the Clinical Safety part of this AR.)

Table 54: Summary of Adjudicated Cardiovascular Endpoints (All Risankizumab – Psoriasis)

Category Preferred Term	Risankizumab 150 mg (N = 1590) (PY = 1681.5)			All Risankizumab (N = 2234) (PY = 2179.0)		
	n (%)	E (E/100 PY)	[95% CI]	n (%)	E (E/100 PY)	[95% CI]
MACE	6 (0.4)	8 (0.5)	[0.21, 0.94]	9 (0.4)	11 (0.5)	[0.25, 0.90]
CV death	3 (0.2)	3 (0.2)		3 (0.1)	3 (0.1)	
Nonfatal myocardial infarction	3 (0.2)	4 (0.2)		5 (0.2)	6 (0.3)	
Nonfatal stroke	1 (< 0.1)	1 (< 0.1)		2 (< 0.1)	2 (< 0.1)	
Extended MACE	10 (0.6)	13 (0.8)	[0.41, 1.32]	13 (0.6)	16 (0.7)	[0.42, 1.19]
CV death	3 (0.2)	3 (0.2)		3 (0.1)	3 (0.1)	
Nonfatal myocardial infarction	3 (0.2)	4 (0.2)		5 (0.2)	6 (0.3)	
Nonfatal stroke	1 (< 0.1)	1 (< 0.1)		2 (< 0.1)	2 (< 0.1)	
Hospitalization for unstable angina	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
Coronary revascularization procedures	3 (0.2)	3 (0.2)		3 (0.1)	3 (0.1)	
Other CV events	12 (0.8)	13 (0.8)	[0.41, 1.32]	13 (0.6)	14 (0.6)	[0.35, 1.08]
Thrombotic events	1 (< 0.1)	1 (< 0.1)		2 (< 0.1)	2 (< 0.1)	
Cardiac arrhythmia	7 (0.4)	7 (0.4)		7 (0.3)	7 (0.3)	
Congestive heart failure	5 (0.3)	5 (0.3)		5 (0.2)	5 (0.2)	

CI = confidence interval; CV = cardiovascular; MACE = major adverse cardiovascular event; PY = patient years

Malignancy

After 52 weeks of exposure, the event rate of malignancies in the risankizumab and ustekinumab treated population was 0.5 E/100 PY. In the All Risankizumab – Psoriasis Analysis Set, 23 (1.0%,1.3E/100PY) subjects had malignant tumours in the initial submission compared with 35 (1.4%; 1.4E/100PY) in the updated safety summary. In the All Risankizumab (150mg) Psoriasis Analysis Set, the event rate for malignant tumours was 1.5/100PY. Fourteen (0.6%) of those 23 subjects had NMSC, including basal cell carcinoma, squamous cell carcinoma of skin, and Bowen's disease, with basal cell carcinoma being the most frequently reported tumour. The exposure-adjusted event rate for basal cell carcinoma and squamous cell carcinoma of skin were 0.6 E/100 PY and 0.2 E/100 PY, respectively. One subject had Bowen's disease (< 0.1 E/100 PY). In the SUR a similar picture was seen .0.7% of subjects had NMSC.The exposure adjusted event rate for basal cell and squamous cell carcinoma was 0.4E/100PY and 0.2E/100PY.

The most frequent non-NMSC malignant tumours were malignant melanoma in situ and prostate cancer that occurred in 2 subjects each (< 0.1 E/100 PY) and breast cancer in 3 subjects (events of breast cancer, invasive ductal breast carcinoma, and invasive lobular breast carcinoma). In the SUR breast and prostate cancer occurred in 3 subjects each (<0.1E/100PY).

Table 55: Summary of Malignant Tumour and Nonmelanoma Skin Cancer AEs (All Risankizumab – Psoriasis Analysis Set)

Category Preferred Term	Risankizumab 150 mg (N = 1590) (PY = 1681.5)			All Risankizumab (N = 2234) (PY = 2179.0)		
	n (%)	E (E/100 PY)	[95% CI]	n (%)	E (E/100 PY)	[95% CI]
Malignant tumors	**21 (1.3)**	**25 (1.5)**	**[0.96, 2.19]**	**23 (1.0)**	**29 (1.3)**	**[0.89, 1.91]**
Basal cell carcinoma	8 (0.5)	9 (0.5)		10 (0.4)	13 (0.6)	
Bowen's disease	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Breast cancer	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Hepatic cancer metastatic	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Intestinal adenocarcinoma	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Invasive ductal breast carcinoma	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Invasive lobular breast carcinoma	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Malignant melanoma in situ	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
Oesophageal carcinoma	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Prostate cancer	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
Squamous cell carcinoma of skin	4 (0.3)	5 (0.3)		4 (0.2)	5 (0.2)	
NMSC	**12 (0.8)**	**15 (0.9)**	**[0.50, 1.47]**	**14 (0.6)**	**19 (0.9)**	**[0.52, 1.36]**
Basal cell carcinoma	8 (0.5)	9 (0.5)		10 (0.4)	13 (0.6)	
Bowen's disease	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Squamous cell carcinoma of skin	4 (0.3)	5 (0.3)		4 (0.2)	5 (0.2)	
Malignant tumors excluding NMSC	**9 (0.6)**	**10 (0.6)**	**[0.29, 1.09]**	**9 (0.4)**	**10 (0.5)**	**[0.22, 0.84]**
Breast cancer	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Hepatic cancer metastatic	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Intestinal adenocarcinoma	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Invasive ductal breast carcinoma	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Invasive lobular breast carcinoma	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Malignant melanoma in situ	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
Oesophageal carcinoma	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Prostate cancer	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	

AE = adverse event; CI = confidence interval; E = events; NMSC = nonmelanoma skin cancer; PY = patient years

Hypersensitivity reactions

Over 16 weeks' hypersensitivity event rates were 10.7 E/100 PYs in the risankizumab 150 mg group, 10.9 E/100 PYs in the placebo group, 5.3 E/100 PYs in the ustekinumab group, and 11.6 E/100 PYs in the adalimumab group. The only notable difference between the placebo and risankizumab groups was the rates of eczema, rash and urticaria associated with risankizumab compared to placebo, which was reported in (0.8%) (0.2%) and (0.5%) of the risankizumab-treated subjects and (0.3%) (0.0%) and (0.3%) placebo-treated subjects respectively. Over 52 weeks event rates were 7.9 E/100 PY in risankizumab 150mg treated group compared with 5.4 E/100 PY for ustekinumab . In the overall Risankizumab 150mg group the event rate was 8.5 E/100 PYs.In the SUR the event rate was 7.1E/100PY. Across both analyses the commonest hypersensitivity AEs (dermatitis contact, eczema, dermatitis, urticaria, and rash) were mild to moderate in severity. No subject exposed to risankizumab in the psoriasis clinical trials experienced anaphylactic reactions or serum sickness-like reactions. In the SUR one patient reported a case of erythema multiforme due to an insect bite. Of note 2 additional cases of anaphylactic reaction were reported in subjects treated with risankizumab for Crohns disease (attributed to IV iron infusion and not considered to be related to study drug) and psoriatic arthritis (considered by investigator to possibly be related to study drug and resulted in discontinuation of study medication.

Following review by the applicant the case was not considered to be related to study drug). No association between hypersensitivity and treatment-emergent anti-drug antibodies was established.

Summary of Hypersensitivity Reaction AEs (All Risankizumab – Psoriasis Analysis Set)

	Risankizumab 150 mg (N = 1590) (PY = 1681.5)			All Risankizumab (N = 2234) (PY = 2179.0)		
	n (%)	E (E/100 PY)	[95% CI]	n (%)	E (E/100 PY)	[95% CI]
Hypersensitivity	**109 (6.9)**	**143 (8.5)**	**[7.17, 10.02]**	**137 (6.1)**	**176 (8.1)**	**[6.93, 9.36]**
Angioedema	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Application site urticaria	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Conjunctivitis allergic	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Cutaneous vasculitis	0	0		1 (< 0.1)	1 (< 0.1)	
Dermatitis	18 (1.1)	19 (1.1)		21 (0.9)	22 (1.0)	
Dermatitis acneiform	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Dermatitis allergic	0	0		1 (< 0.1)	1 (< 0.1)	
Dermatitis atopic	3 (0.2)	3 (0.2)		3 (0.1)	3 (0.1)	
Dermatitis contact	25 (1.6)	32 (1.9)		31 (1.4)	38 (1.7)	
Drug eruption	1 (< 0.1)	1 (< 0.1)		2 (< 0.1)	2 (< 0.1)	
Drug hypersensitivity	3 (0.2)	3 (0.2)		4 (0.2)	4 (0.2)	
Eczema	23 (1.4)	24 (1.4)		24 (1.1)	26 (1.2)	
Erythema multiforme	0	0		2 (< 0.1)	2 (< 0.1)	
Face oedema	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Hand dermatitis	3 (0.2)	3 (0.2)		4 (0.2)	4 (0.2)	
Hypersensitivity	2 (0.1)	2 (0.1)		2 (< 0.1)	2 (< 0.1)	
Lip swelling	0	0		2 (< 0.1)	3 (0.1)	
Multiple allergies	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Pharyngeal oedema	1 (< 0.1)	3 (0.2)		1 (< 0.1)	3 (0.1)	
Pruritus allergic	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Rash	8 (0.5)	9 (0.5)		11 (0.5)	12 (0.6)	
Rash generalised	0	0		1 (< 0.1)	1 (< 0.1)	
Rash pruritic	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Rhinitis allergic	6 (0.4)	6 (0.4)		9 (0.4)	10 (0.5)	
Skin reaction	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Swelling face	2 (0.1)	2 (0.1)		3 (0.1)	3 (0.1)	
Urticaria	16 (1.0)	25 (1.5)		19 (0.9)	28 (1.3)	
Urticaria cholinergic	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	
Urticaria chronic	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	1 (< 0.1)	

Depression and suicidal ideation and behaviour (SIB)

In the Primary Safety Pool, the depression event rates in the risankizumab150 mg group and placebo group were 1.0 E/100 PY and 2.2 E/100 PY, respectively. Depression event rates were 1.1 E/100 PYs in the adalimumab group and 2.6 E/100 PYs in the ustekinumab group. Overall the depression event rate was 1.2 E/100 PYs in the risankizumab 150 mg group. In the SUR (All Risankizumab psoriasis analysis set) the depression event rate was 0.9E/100PY.

There were no completed suicides in the risankizumab treated population. In the Primary Safety Pool, the SIB event rates were 0.5 E/100 PYs in the risankizumab 150 mg group, 1.1 E/100 PYs in the placebo group, 1.3 E/100 PYs in the ustekinumab group, and 1.1 E/100 PYs in the adalimumab group.One subject had a self-injurious ideation AE that was not serious and 1 subject had a suicide attempt that was serious. Both events of SIB were in subjects with multiple confounding factors. The applicant has indicated that the SIB event rate (< 0.1 E/100 PY) is comparable to other recent clinical development programs (guselkumab 0.10/100 subject-yrs., secukinumab, 0.06/100 subject-yrs.; ixekizumab, 0.14/100 subject yrs.) .There were no new cases of suicidal ideation and behaviour in the SUR.

Adverse Drug Reaction

Following a review of aall AEs reported during the 16-week controlled periods of the Phase 2 and Phase 3 clinical studies and a review of events with longer latency and rare events in the 52 week Ustekinumab-Controlled Analysis Set, the OLE study data, and SAE reports from other indications, the

Sponsor considers the following events to be adverse drug reactions (ADRs): upper respiratory infections, headache, fatigue, injection site reactions, tinea infections, and folliculitis. Cough and pruritus occurred at a rate of ≥ 1% of subjects in the risankizumab group with a higher rate than the placebo group during the 16-week controlled period of pooled studies. These terms have been included as ADRs or justification for their exclusion should be provided.

Serious adverse events and deaths

Serious adverse events

In the primary safety pool (16 weeks), Thirty-one (2.4%) subjects in the risankizumab 150 mg group (9.9 E/100 PY), compared to 12 (4.0%) subjects in the placebo group (17.4E/100 PY), 12 (5.0%) subjects in the ustekinumab group (18.4 E/100 PY), and 9(3.0%) subjects in the adalimumab group (14.7E/100 PY) had SAEs. Five subjects treated with risankizumab had SAEs that were assessed by the investigators as possibly being related to study drug: drug-induced liver injury, liver injury, cellulitis, herpes zoster, osteomyelitis, and asthma. SAEs resulting in discontinuation of study drug were cardiac failure congestive, drug-induced liver injury, liver injury, invasive lobular breast carcinoma, and oesophageal carcinoma.

After 52 weeks of exposure, 42 (7.0%) subjects in the risankizumab 150mg group had SAEs (9.4E/100 PY) compared to 18 (9.0%) subjects in the ustekinumab group (10.9E/100PY). SAEs reported by more than 1 risankizumab-treated subject were cardiac failure congestive, coronary artery disease, cellulitis, pneumonia, sepsis, basal cell carcinoma, and abortion spontaneous (2 subjects each). 8 (1.3%) subjects in the risankizumab group had SAEs in the cardiac disorder SOC compared to 1 (0.5%) subject in the ustekinumab group. 5 subjects had SAEs assessed by the investigators as being possibly related to study drug 1 subject each had drug-induced liver injury, herpes zoster, and pneumonia; 1 subject had cellulitis and osteomyelitis; and 1 subject had pyelonephritis and sepsis.

In the All Risankizumab 150mg Group 6.9% had SAEs (9.9 E/100 PY) compared with 8.3% (9.3E/100PY) of subjects in the SUR (All Risankizumab Psoriasis Analysis Set). The most frequently reported SAEs (≥ 3 All Risankizumab subjects) were basal cell carcinoma, sepsis, cellulitis, pneumonia, coronary artery disease, transient ischemic attack, squamous cell carcinoma of skin, cardiac failure congestive, and myocardial infarction. New SAEs reported ≥3 subjects in the SUR acute MI, breast cancer, cholecystitis, cholelithiasis, depression, erisypelas, fall, ischaemic stroke, osteoarthritis, prostate cancer and syncope. Infections and infestations was the SOC with the highest number of subjects with SAEs. Overall SAEs were most commonly reported in the Cardiac Disorders Infections, Neoplasm and Hepatic Disorders SOC across all three analyses populations. Overall a total 23 subjects, 16 of whom were treated with risankizumab 150mg had SAEs assessed by the investigator as possibly being related to study drug compared with 1.6%; 1.5E/100PY in the SUR. Most SAEs assessed as related by the investigator occurred in 1 subject. The SAEs which occurred in more than 1 subject were cellulitis, erysipelas, herpes zoster, osteomyelitis, pneumonia, urinary tract infection, and basal cell carcinoma (2 subjects each) and sepsis (5 subjects 3 of whom were treated with RZB150mg). Two notable SAEs that occurred in the SUR were one case of autoimmune encephalitis and one case of demyelination. The case of autoimmune encephalitis was not confirmed. There are limited details and relationship to study drug is not discussed. The case of demyelination was reported in a subject (with a history of focal demyelinating changes at baseline), approximately 9 months after starting therapy with risankizumab. The investigator considered the event as having a reasonable possibility of being related to study drug whereas the applicant considered there was no reasonable possibility of the event being related to study drug.

Summary of SAEs Occurring in ≥ 2 Subjects in the All Risankizumab Group (All Risankizumab – Psoriasis Analysis Set)

System Organ Class Preferred Term	Risankizumab 150 mg (N = 1590) (PY = 1681.5) n (%)	 E (E/100PY)	All Risankizumab (N = 2234) (PY = 2179.0) n (%)	 E (E/100PY)
Any adverse event	109 (6.9)	167 (9.9)	139 (6.2)	213 (9.8)
Cardiac disorders				
Acute myocardial infarction	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Angina unstable	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Atrial fibrillation	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Cardiac failure congestive	3 (0.2)	3 (0.2)	3 (0.1)	3 (0.1)
Coronary artery disease	4 (0.3)	5 (0.3)	4 (0.2)	5 (0.2)
Coronary artery occlusion	0	0	2 (< 0.1)	2 (< 0.1)
Myocardial infarction	2 (0.1)	2 (0.1)	3 (0.1)	3 (0.1)
Infections and infestations				
Cellulitis	5 (0.3)	5 (0.3)	5 (0.2)	5 (0.2)
Erysipelas	0	0	2 (< 0.1)	2 (< 0.1)
Herpes zoster	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Osteomyelitis	2 (0.1)	2 (0.1)	2 (<0.1)	2 (< 0.1)
Pneumonia	3 (0.2)	3 (0.2)	4 (0.2)	4 (0.2)
Pyelonephritis	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)
Sepsis	5 (0.3)	5 (0.3)	7 (0.3)	7 (0.3)
Urinary tract infection	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)
Injury, poisoning and procedural complications				
Fall	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Metabolism and nutrition disorders				
Dehydration	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Musculoskeletal and connective tissue disorders				
Arthralgia	2 (0.1)	3 (0.2)	2 (< 0.1)	3 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basal cell carcinoma	7 (0.4)	7 (0.4)	9 (0.4)	11 (0.5)
Prostate cancer	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Squamous cell carcinoma of skin	4 (0.3)	5 (0.3)	4 (0.2)	5 (0.2)
Nervous system disorders				
Hemiplegia	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Ischaemic stroke	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)
Transient ischaemic attack	1 (< 0.1)	1 (< 0.1)	4 (0.2)	4 (0.2)
Pregnancy, puerperium and perinatal conditions				
Abortion spontaneous	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Psychiatric disorders				
Depression	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Respiratory, thoracic and mediastinal disorders				
Respiratory failure	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Surgical and medical procedures				
Abortion induced	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)
Vascular disorders				
Hypertension	2 (0.1)	2 (0.1)	2 (< 0.1)	2 (< 0.1)

Deaths

In the original safety summary, deaths were reported in 5 male subjects treated with risankizumab and 2 subjects treated with adalimumab. An additional 5 new deaths were reported in the SUR .

Of the 5 deaths reported in the original application in risankizumab-treated subjects, 4 were treatment-emergent (i.e., occurred within 105 days after the last dose of risankizumab). There were no deaths in the clinical studies conducted in other (non-psoriasis) indications. Four of the deaths occurred >50 days after the last dose of study drug. One death was reported 9 days following last dose of risankizumab 150mg (acute myocardial infarction [MI]). Of the 5 deaths, 2 were adjudicated as cardiac deaths (Acute MI and sudden cardiac death) however one of these was later attributed to a drug overdose, 2 were due to unknown cause, and 1 was a cancer death. The two cases attributed as 'due to unknown cause', had complex background cardiovascular comorbidities and in the absence of an alternative aetiology, are likely to be cardiac in nature.

Table 56: Listing of All Deaths in Phase 2/3 Psoriasis Studies

Study Number	Subject Number	Age/Sex/ Race	Treatment Group	Onset Day[a]/ Days Since Last Dose	Cause of death Preferred Term[b] (Adjudicated Term)	Comment
M16-010	[redacted]		ADA	61/32	Gallbladder cancer (non-cardiac death)	Subject was on brodalumab for over 2 years prior to taking adalimumab. Short time to cancer diagnosis suggests lack of temporal plausibility.
			ADA	113/7	Sepsis/Abdominal abscess (non-cardiac death)	Subject had concurrent diabetes. Sepsis and abdominal abscess immediately following cholecystectomy and repair of gastric perforation.
			RZB 150 mg	73/9	Acute myocardial infarction (death due to acute MI)	Subject had pre-existing MI, PCI with stent placement (approximately a year prior), stroke, TIA, diabetes, hypertension, chronic heart failure, dyslipidemia, cardiac hypertrophy.
M15-995			RZB 150 mg	189[c]/161 Not treatment-emergent	Death (undetermined death)	Subject had concurrent CAD, COPD, left bundle branch block, sleep apnea, and hypertension. Patient developed CHF and angina and underwent percutaneous transcatheter coronary angioplasty.
			RZB 150 mg	385/101	Seizures (sudden cardiac death)	Late-breaking information received post-adjudication indicates that cause of death was due to drug overdose (cocaine and oxycodone).
M15-992			RZB 150 mg	263/66	Death (undetermined death)	Subject had pre-existing hypertension, morbid obesity, diabetes, and hypercholesterolemia and possible MI.
			RZB 150 mg	224/55	Metastatic cancer of liver (non-cardiac death) Adenocarcinoma from bowel (non-cardiac death)	Metastasis of the tumor from bowel to liver indicates long standing existence of the cancer and temporal implausibility.

ADA = adalimumab; AV = atrioventricular; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; F = female; M = male; MI = myocardial infarction; PCI = percutaneous coronary intention; RZB = risankizumab; TIA = transient ischemic attack

a. Onset day is the number of days since first dose of risankizumab.

b. Preferred terms reported as having an outcome of death.

c. This death was not treatment-emergent as it occurred on Study Day 189 (161 days after last dose, outside of the treatment-emergent window of 105 days).

Five new deaths were reported as of the SUR data cutoff, all of which occurred in psoriasis studies in subjects treated with risankizumab. The 5 new deaths all occurred in male patients ranging in age from 37 to 74 years of age. Cause of death was, epileptic seizure(undetermined death),death(adjudication pending), pancreatitis(undetermined death),cardiac arrest (adjudication pending) and cardiac failure (adjudication pending). All of the deaths occurred 14-88 days after the last dose of study drug. One death was reported 14 days following last dose of risankizumab 150mg (pancreatitis undetermined death). The five new deaths are highlighted in bold in the table below.

Laboratory findings

For haematology, mean changes from Baseline with risankizumab treatment groups were small and were not considered to be clinically meaningful. Rates were comparable to adalimumab and ustekinumab with no significant differences to placebo at 16 weeks. Following longer term exposure CTC toxicity grade 3 was noted for decreased Hb 1 case, platelets 1 case , leucocytes 4 cases, lymphocytes 6 cases) Grade 4 CTC toxicity values were observed for neutrophils decreased and lymphocytes decreased in 1 subject each. There were no significant increases in the frequencies of clinically important haematology values between the initial submission and the SUR.

For clinical chemistry, mean changes from Baseline with risankizumab treatment groups were small and were not considered to be clinically meaningful. Rates were comparable to adalimumab and ustekinumab with no significant differences to placebo at 16 weeks.

The most common CTC grade ≥3 clinical chemistry abnormalities over long term exposure in the risankizumab group were elevations in glucose, and triglyceride elevations, which occurred in 4.2%, and 4.7%, respectively, of subjects in the risankizumab treated group. Increased levels of triglycerides CTC Grade ≥ 3 (>5.7mmol) were recorded in 89 subjects and 13 had readings >11.4 mmol/L. 86 patients had CTC Grade ≥ 3 blood glucose >13.9 mmol/L. There were 8 reports (0.6%) of creatine kinase increased and3 reports (0.2%) of a CTC AE toxicity grade 4 at 16 weeks. The overall percentage of grade 3 events (0.9%) and the percentage of grade 4 events (0.6%) increased over longer term exposure. There were 3 reports of a CTC AE toxicity grade 4 chemistry abnormality (elevated ALT two cases and AST one case), all of which occurred within 16 weeks of starting treatment. AST and ALT elevation ≥ 5 ULN were reported in <1% of subjects. There were 2 subjects with ALT elevation of > 20 × ULN. Subjects also had AST elevation of > 20 × ULN) associated with a drug induced liver injury (SAE). This case was identified as an adverse event of special interest. Subject who were treated with 90 mg risankizumab had a history of fatty liver. The elevation resolved after 2 weeks. This was not considered to be an SAE. No cases in the risankizumab psoriasis safety population fell into the possible Hy's law range.

Of note an additional case in the Phase 2 psoriatic arthritis study met the laboratory criteria for Hy's law 56 days after the last dose of study drug (risankizumab 150 mg at Week 0 and Week 12). The case was considered by the investigator to be related to study drug. The case was confounded by a history of fatty liver; baseline elevated liver enzymes and ongoing alcohol abuse. The MAH considered the AEs as having no reasonable possibility of being related to study drug. The events were reported resolved at the end of the study.

Rates of potentially clinically relevant clinical chemistry values were comparable between the original safety review and the updated safety report. The most common CTC grade ≥3 clinical chemistry abnormalities in the risankizumab group in the SUR were elevations in glucose, and triglyceride elevations, which occurred in 4.7%, and 5.9%, respectively, of subjects in the risankizumab treated group. The proportion of patients with clinically important LFT elevations remained low. One additional subject met the criteria for Hy's law. A subject with a history of cardiac disease, hypertension, obesity, anxiety obesity and atrial fibrillation who reported abnormal LFTs (ALT 4 times ULN : AST 3 times ULN:ALK phos 0.5 times ULN and total bilirubin 2 times ULN) at day 575. The applicant assessed the liver enzyme elevation as being related passive hepatic congestion secondary to worsening heart failure.

Two additional cases of AST values 10-20 times ULN were reported both occurring in women. Both cases were described as having reasonable possibility of being related to study drug. The first case was confounded by treatment with nitrofurantoin. No other cause was identified for the second case. Additional information is being sought by the applicant.

There was no evidence for any clinically meaningful changes from baseline in QT interval values in the pooled safety analysis sets. No cases of Torsade de pointes/QT prolongation were reported as AEs.

Overall a rather small proportion of subjects experienced increased systolic or diastolic blood pressure potentially clinically important vital sign abnormalities. A total of 5.5% of subjects exhibited systolic blood pressures ≥160mm Hg and ≥20mm Hg change from baseline systolic blood pressure compared with 6.8% in the SUR. Justification of BP and BP change threshold values was provided by the Applicant and are discussed below.

The AbbVie definition of a potentially clinically significant increase in systolic and diastolic BP values was guided by the grade 3 hypertension definition in CTCAE v4.03 (systolic BP above 160 mmHg or diastolic BP above 100 mmHg). There is a difference of 5 mmHg in the potentially clinically significant diastolic blood pressure (BP) elevation cutoff between the CTCAE and the Applicant's definition (> 100 mmHg for grade 3 per CTCAE definition versus > 105 mmHg for Grade 3 per the Applicant's definition). Since roughly the one-third of psoriasis patients in PSO Phase-3 studies had hypertension at baseline, the Applicant's definition for threshold values of the potentially clinically significant systolic and diastolic BP might be acceptable.

The clinically important BP *change* threshold values were based on the *2018 ESC/ESH guidelines for the management of arterial hypertension* (European Heart Journal, Volume 39, Issue 33, 1 September 2018, Pages 3021–3104) on one hand and on the *NCI CTCAE definition of grade 2 hypertension* on the other hand. In the ESC/ESH Guideline, the thresholds for the *change in the categories* of hypertension are based on a 20 mmHg change in SBP and a 10 mmHg change in DBP (Table 33). The NCI CTCAE definition of grade 2 hypertension includes symptomatic increase of diastolic blood pressure by >20 mmHg. Thus, the 15 mmHg threshold for DBP chosen by the Applicant falls between the CTCAE guidance of 20 mmHg increase in DBP and the ESH between-category difference of 10 mmHg in DBP.

Table 57:Classification of Office Blood Pressure and Definitions of Hypertension Grade (*2018 ESC/ESH guidelines for the management of arterial hypertension)*

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

BP = blood pressure; SBP = systolic blood pressure.
[a] BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
[b] Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.
The same classification is used for all ages from 16 years.

Further, Applicant performed an updated analysis of DBP data using a cutoff of ≥100 mmHg (i.e. grade 3 Hypertension per CTCAE definition) and an increase of ≥10 mm Hg for the DBP cutoff based on the ESH hypertension categories (Table 34).

Table 58:Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Important Diastolic Blood Pressure

	Primary Safety Pool				Ustekinumab-controlled Pupulation	
Criteria	Placebo (N=300) n (%)	Ustekinumab (N=239) n (%)	Adalimumab (N=304) n (%)	Risankizumab 150 mg (N=1306) n (%)	Ustekinumab (N=199) n (%)	Risankizumab 150 mg (N=598) n (%)
Original Analysis: ≥ 105 mmHg and ≥ 15 mmHg increase	5 (1.7)	3 (1.3)	8 (2.6)	10 (0.8)	5 (2.5)	9 (1.5)
Updated Analysis: ≥ 100 mmHg and ≥ 10 mmHg increase	15 (5.0)	9 (3.8)	22 (7.2)	47 (3.6)	14 (7.0)	46 (7.7)

According to this updated analysis, proportions of patients with potentially clinically important DBP and DPB change values increased with the decreased cutoff values for all treatment groups. Comparison of proportions of patients concerned for different treatment groups shows that the *between-treatment group* ratios of patients with potentially clinically important DBP and DPB change values are rather similar.

The only exception is the Risankizumab 150 mg group in the Ustekinumab-controlled population, where the 7.7% of proportion of patients with potentially clinically important DBP and DPB change values seems to be somewhat higher than expected. (For example, according to the *original* analysis, 0.8% and 1.5% of the Risankizumab 150 mg patients in the Primary Safety Pool and the Ustekinumab-controlled population, respectively had DBP higher than 105 mmHg with a DBP increase higher than 15 mmHg. According to the *updated* analysis, the proportions of Risankizumab 150 mg patients experiencing DBP higher than 100 mmHg with a DBP increase higher than 10 mmHg are 3.6% and 7.7% for Primary Safety Pool and the Ustekinumab-controlled population, respectively. Further, according to the *original* analysis, potentially clinically important DBP and DPB change values were experienced by 2.5% and 1.5% of the Ustekinumab and Risankizumab 150 mg patients, respectively in the *Ustekinumab-controlled* population. The *updated* analysis showed an opposite relationship with incidence of potentially clinically important DBP and DPB changes of 7.0% for *Ustekinumab* treatment group and 7.7% for *Risankizumab 150 mg* treatment group.)

However, these comparisons should be handled with caution due to the small number of patients concerned in the original DBP analysis setting (DBP higher than 105 mmHg with a DBP increase higher than 15 mmHg).

In summary, Applicant's justification for BP and BP changes threshold values can be accepted.

Safety in special populations

Gender

Treatment-emergent AEs reporting rates were slightly higher in females (53%) compared with males (47%) at 16 weeks. A similar picture was seen over longer term exposure to risankizumab 150mg 79% females compared with males 73% males experienced treatment emergent adverse events. The proportions of subjects with SAEs, or who discontinued due to an AE in the risankizumab group was generally similar among men and women for each over the short and longer term exposure. All five deaths following treatment with risankizumab occurred in males.

Age

The overall rates of AE experienced in subjects ≥ 65 years of age and are comparable to the overall population however higher rates of SAEs, AEs leading to discontinuation, and severe AEs were higher in the elderly population.

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age >= 75 YEARS number (percentage)
Total AEs	1062 (75.1)	113 (72.4)	15 (75.0)
Severe AEs	76 (5.4)	13 (8.3)	2 (10.0)
Serious AEs – Total	88 (6.2)	19 (12.2)	2 (10.0)
- Fatal	4 (0.3)	1	0
AE leading to drop-out	25 (1.8)	4 (2.6)	0

Baseline static Physician's Global Assessment and body weight

Impact of Baseline static Physician's Global Assessment (sPGA; 3, 4), and body weight (≤ 100 kg, ≥ 100 kg) on the overall safety profile of risankizumab should be summarised and presented for review. (LOQ).

Previous use of psoriasis therapies

Analysis by previous use of psoriasis therapies only included Prior TNF inhibitor use. There were no clinically meaningful differences in safety between subjects who were TNFi naïve or experienced for AEs, SAEs, AEs leading to discontinuation, and severe AEs. Of note two deaths occurred in prior TNFi population. Prior treatment with phototherapy or prior use of nonbiologic systemics should also be presented.

Immunological events

The effect of immunogenicity (ADA or anti-risankizumab antibodies) on risankizumab safety was assessed using treatment-emergent adverse events in relevant areas of safety interest, which include hypersensitivity reaction and injection-site reactions. The incidence of injection site reactions for the Primary Safety Pool was higher among ADA positive (2.7%) than the ADA negative (1.3%). The incidence of hypersensitivity reactions for the Primary Safety Pool was comparable among antidrug antibody positive (2.3%) and the antidrug antibody negative (3%) subjects. Across 52 weeks of exposure, the incidence of injection site reactions was 5% among ADA positive subjects and 3.3% for the ADA negative subjects. The incidence of hypersensitivity reactions was 7.6% vs. 7% in ADA-positive vs. ADA-negative subjects across 52 weeks of risankizumab exposure. In the original application ADAs were only evaluated for up to 52 weeks exposure as ADA data were not available from the OLE studies for this period of time.

Comparison of Hypersensitivity Reaction and Injection-Site Reaction by ADA Status for ADA Subset of All Risankizumab Psoriasis Analysis Set

	ADA Subset of All Risankizumab Psoriasis Analysis Set*			
	Risankizumab 150 mg SC Dose (N = 1590)		All Risankizumab Doses (N = 1807)	
	ADA Positive (N = 377)	ADA Negative (N = 1213)	ADA Positive (N = 420)	ADA Negative (N = 1387)
hypersensitivity reaction (per SMQ), n (%)	31 (8.2%)	78 (6.4%)	32 (7.6%)	97 (7.0%)
injection site reaction (per CMQ), % (n/N)	17 (4.5%)	42 (3.5%)	21 (5.0%)	46 (3.3%)

Note: Risankizumab exposure through the end of the studies (Studies 1311.2, M16-008 [Study 1311.3], M15-995 [Study 1311.28] and M16-010 [Study 1311.30]) or until data-cut for interim analysis M15-992 (Study 1311.4).

Safety related to drug-drug interactions and other interactions

The potential for drug-drug interactions between risankizumab and CYP450 enzyme activity, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A using their probe substrates was assessed in the Phase 1 Study M16-007(1311.36). Based on the results of this study, no dose adjustments are required for the drugs that are substrates of these CYP enzymes during co-administration with risankizumab. Additionally, population PK analyses indicated that the clearance of risankizumab was not impacted by common concomitant medications (antihypertensives, antihyperlipidemics, antidiabetics, analgesics, and levothyroxine) used in the Phase 3 studies by subjects with plaque psoriasis. These PK results are discussed in the Clinical Pharmacology section.

Discontinuation due to AES

Over the 16 week primary safety analysis period < than 1% of subjects (2.7 E/100PY) in the risankizumab 150 mg treatment group discontinued study drug due to AEs. This was comparable with ustekinumab (1.3%) and adalimumab (2.0%). Discontinuations in the placebo group were higher (3.0%) due to the subjects who discontinued due to psoriasis (7 [2.3%] subjects). No TEAEs leading to discontinuation of study drug were reported in more than 1 risankizumab-treated subject. The AEs leading to discontinuation of study drug that were also SAEs were cardiac failure congestive, drug-induced liver injury, liver injury, invasive lobular breast carcinoma, and oesophageal carcinoma. Over 52 weeks 0.8% (0.8E/100PY) of the risankizumab treated group compared with 2% (2E/100PY) of the ustekinumab treated group discontinued study drug. The AEs leading to the discontinuation of risankizumab treatment in 5 subjects included cardiac failure congestive, oedema peripheral, drug-induced liver injury, pneumonia, and vasculitis. In the All Risankizumab 150mg Analysis population 1.8% of risankizumab treated patients (2.2 E/100PY) discontinued due to an AE. The AEs leading to discontinuation of study drug that were also SAEs were lymphadenopathy mediastinal, cardiac failure congestive, drug-induced liver injury, liver injury, pneumonia, sepsis, arthralgia, muscular weakness, hemiplegia, and all the AEs reported in the Neoplasms benign, malignant and unspecified SOC. The discontinuations due to chronic hepatitis B, hepatitis B, and human immunodeficiency virus (HIV) were in asymptomatic subjects who tested positive at the time of the annual infection screening and were discontinued per protocol.

2.6.1. Discussion on clinical safety

The applicant conducted an integrated safety analysis based on 3 key safety pools which included the phase 2, phase and open label studies. These datasets have a rational basis and the pooled reporting is

consistent with that from the separate studies. The groups provide short and longer term comparative data with longer term uncontrolled data up to 77 weeks. Three studies were ongoing at the data cut-off date M15-997 (n=1392/2000); Study M16-009 (N=110) Study; M15-992 ongoing N=507/500. The applicant has submitted a safety update report (SUR) updating the original Clinical Summary of Safety. This SUR provides approximately 7 months of additional safety data from the original data cut-off in 01 Sep 2017 up to 29 March 2018. This data originated from Study M15-997, M15-992 and Study M16-009.

Exposure

With over 1590 patients exposed for up to 77 weeks the ICH E1 safety exposure requirements of >1500 patients exposed (300 to 600 for 6 months, > 100 for 1 year) were met. In the primary safety pool the number of patients in the comparator arms was small compared to risankizumab 150mg recipients (RZB 150 mg (N=1306) UST (N=239) Adalimumab (N=304) PBO (N= 300).

In the ustekinumab controlled population there was an imbalance in the numbers of patient who were treated with risankizumab compared to ustekinumab (RZB 150 mg (N=598) UST (N = 199)) however this analysis does provide some information on the safety of risankizumab compared with ustekinumab at 52 weeks in subjects with psoriasis. The All Risankizumab –Psoriasis (N = 2234) assesses the risankizumab exposure over 77 weeks. It also includes an overview of safety at higher dosages and lower dosages of risankizumab (90mg and 180mg). Exposure adjusted analysis could be acceptable in addressing the imbalance in numbers in the various treatment groups.

In the original application 2,234 patients received at least 1 dose of risankizumab representing 2167 PY of exposure. The SUR includes data from an additional 237 subjects that representing an additional 1185 PY of exposure for a total of 3352 PY of exposure. In total 68% were exposed to risankizumab for for at least 1yr, 7% for at least two years 3.4% had ≥ 3 years of risankizumab treatment. . Due to the risk of side effects with a long induction period (e.g. malignancy, MACE) long term safety data has been identified as missing data for the RMP.

Subject Disposition

Completions rates were high across all three analysis groups. <2% of subjects discontinued due to AEs across the three safety analysis populations. Male and female patients > 18 years of age with moderate to severe plaque psoriasis, poorly controlled by topical treatments, systemic treatments (either non-biologic or biologic), or phototherapy were recruited to the phase 2 and 3 studies. Patients with latent TB, active ongoing cardiovascular, hepatic disease, treated basal cell carcinoma and patients who were 5 years' period remission free from other malignancies were eligible for recruitment to these studies. This is similar to patient population recruited to studies for similar type treatment for psoriasis.

Demographic characteristics

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. Eighty percent of participants were white, 3% Black or African Americans. Approximately one third of participants were female, 10 % of subjects were between 65 and 74 years of age. Under representation of females, Black or African Americans and subjects over 65years was not shown to impact on the generalisability of the outcomes.

Adverse events

In the first 16 weeks of the Phase 2 and 3 psoriasis studies (Primary Safety Pool), the incidence rates of overall AEs and SAEs were comparable to the rates with placebo and more favourable than those seen with ustekinumab and adalimumab. The rates of AEs leading to discontinuation of study drug were low overall and occurred at a lower rate in the risankizumab 150 mg group (2.7E/100PY) compared to placebo (9.8E/100PY) ustekinumab (4.0E/100PY) and adalimumab (6.3E/100PY). Exposure-adjusted TEAE rates for risankizumab 150mg calculated as events/100 PY tended to decrease across the three safety analysis populations with longer exposure(318 E/100PY at 16 weeks; 228E/100PY at 52 weeks and 246E/100PY up to 77 weeks).

In the primary safety pool, representing the first 16 weeks of treatment in the phase 2 and 3 studies, upper respiratory tract infections, viral upper respiratory tract infections, headache, arthralgia, and fatigue were the commonest AEs 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 AEs in the adalimumab group. ISRs like injection site erythema, pruritus, pain and swelling were lower for the risankizumab group.

At 52 weeks the most frequently reported AEs (≥ 2% of subjects) reported with risankizumab treatment were viral upper respiratory tract infection, upper respiratory tract infection, arthralgia, headache, hypertension, fatigue, gastroenteritis, diarrhoea, back pain, influenza, sinusitis and folliculitis.

In the overall risankizumab 150mg 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. In general, the rates for AEs through Week 16 to 77 were similar with the highest frequency of AEs in the infections SOC across the three analysis periods. The majority of AEs including infections was of mild to moderate severity and was self-limiting and didn't result in discontinuation of study medication.

Rates of severe AEs were comparable across the three analysis sets. (Primary safety pool 9E/100 PY; 52 week ustekinumab controlled group 7.6E/100 PY; and all risankizumab safety pool 8.5E/100PY). The SOCs with the highest number of severe events were Cardiac disorders SOC, Infections and infestations SOC and gastrointestinal disorders and hepatic disorders SOC. Treatment-related adverse events occurred in 12% of risankizumab group at week 16 which was higher than placebo but lower than adalimumab or ustekinumab treated patients over the same period. Approx. 20% of the 52 week ustekinumab controlled risankizumab 150mg treated group and the All-risankizumab 150mg treated population reported treatment related AEs. The treatment related adverse event profiles are similar across all three safety populations with the exception of injection site erythema which is reported at 52 weeks and in the long term safety population.

No information has been provided on the emergence of adverse event rates over time. A summary of AEs/SAEs by 3 month intervals/treatment cycle was provided over the entire treatment period Over repeat treatments the safety profile remains generally stable with an overall trend towards reduced incidence of serious adverse events and AEs in areas of special interest (ASI) over longer term treatment. No new safety concerns have been identified following review of the safety summary for SAEs and AEs over 90-180-day time intervals.

Serious adverse events and deaths

After 16 weeks the SAE event rate was markedly lower for the risankizumab 150 mg group at 9.9E/100PY compared with the placebo group at 17.4E/100PY, ustekinumab at 18.4 E/100PY and adalimumab groups group at 14.7E/100PY.

At 52 weeks the exposure adjusted SAE rate for risankizumab 150mg was slightly lower at 9.4E/100PY compared with 10.9E/100PY for ustekinumab over the same period. The overall event rate for subjects exposed to risankizumab 150g up to 77 weeks with serious adverse events was also 9.9E/100PY. The exposure adjusted SAEs rate in the risankizumab 150mg treated groups was comparable across three analysis periods. The rate of serious AEs (SAEs) also did not increase between the CSS (All Risankizumab – Psoriasis Analysis Set) (9.8 E/100 PY) and the SUR (9.3 E/100 PY). At 16 weeks the exposure adjusted event rate in the primary safety pool is much lower for risankizumab 150mg compared with the comparator groups. The ustekinumab exposure adjusted SAE rate is almost double that at 52 weeks. This was attributed by the applicant to the different study populations included in the 16 week and 52 week analyses. Overall these findings don't impact on the determination of the safety profile for Risankizumab. This issue will not be further pursued. The most frequently reported SAEs in risankizumab treated subjects were infection-related events, cardiac events and neoplasms. Overall 1% of the risankizumab population had treatment related SAEs. The treatment-related SAE s were most frequently reported for the Infections and infestations SOC. These were mainly bacterial infections including pneumonia, sepsis, osteomyelitis and cellulitis. Despite the serious nature of these infections study medication was only discontinued for 1 case of pneumonia and 1 case of sepsis. The rate of discontinuation of risankizumab due to AEs was unchanged in the SUR. (See discussion on adverse events of special interest)

There were 5 deaths in risankizumab treated patients in the original safety review. All occurred in males between the age of 32 yrs. and 70yrs. Four of the 5 deaths were originally adjudicated as CV deaths and 1 death was due to malignancy. Three of the deaths (acute MI, cause undetermined 2 cases) occurred in subjects with multiple cardiac risk factors and were likely to have had a cardiac cause. The remaining death was attributed to a drug overdose. All of the deaths were considered by the Applicant to be unrelated to study treatment. One death was reported 9 days following last dose of risankizumab 150mg. Four occurred >50 days after the last dose of study drug. The lack of a temporal association undermines any possible link with risankizumab treatment. There were no adjudicated CV deaths in placebo, ustekinumab or adalimumab groups. All of these deaths were confounded by past CV history. In the SUR, 5 additional deaths were reported in subjects receiving Risankizumab (Preferred Terms of epileptic seizure, pancreatitis, cardiac arrest, cardiac failure, and death), for a total of 10 deaths. Two and possibly a third death (adjudication pending) were cardiovascular. These are currently being adjudicated. The two other deaths pancreatitis and epileptic seizure are likely explained by underlying medical issues. No trend or pattern in type or cause of mortality could be discerned. The mortality rate in the All Risankizumab arm (i.e., any subject treated with risankizumab regardless of dose) of the All Risankizumab Psoriasis Population through the SUR cut-off was 0.3 events per 100 patient-years. The applicant calculated an SMR of 0.659 (95% CI: 0.315 to 1.211) using the raw number of deaths and the expected annual death rate yield. This calculation suggests that the 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 interests evaluated were infections, malignancies, cardiovascular events, hepatic events, injection site and immune reactions, Depression and Suicidal behaviors. With additional safety data from the SUR (data cutoff 29March 2018), no new important risks have been identified compared with the initial submission.

The rate of infection events for subjects treated with risankizumab 150mg was lower than adalimumab but higher when compared with placebo and ustekinumab over week 16 and 52. Comparing the exposure adjusted incidences of infections between the Primary safety pool (16 weeks) and the Ustekinumab controlled group (52 weeks) for subjects treated with risankizumab 150mg (90.8E/100PY vs. 73.9E/100PY) suggests a reduction in infections over the longer exposure. The exposure adjusted infection rate for the overall risankizumab 150mg treated group (75.5E/100PY) 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%). The overall rate of serious infection with the additional cohort of patients in the SUR reduced from 1.8/E/100PY 95% CI 1.27, 2.45 (PY=2179.0) to 1.4E/100PY 95% (PY=3404.7). Similar to the original CSS, the most common serious infections in the tabulated summary of serious infections in the SUR were gastrointestinal infections, sepsis, urosepsis, skin infections and lower respiratory tract infections.This included a number of serious bacterial infections including 5 reports of cellulitis and 7 reports of sepsis and 5 of pneumonia and 2 cases of osteomyelitis. Disruption of the IL23/IL17 axis and its impact on the risk for the development of serious infections such as sepsis, cellulitis, and pneumonia was further discussed by the applicant. The applicant provided a very brief overview of the literature describing the impact of IL-23 blockade on host defences against acute bacterial and Herpes Zoster Infections. Some evidence is presented describing the role of IL-23 in early host resistance to klebsiella, toxoplasmosis and GI pathogens. Lack of IL-p19 subunit does not appear to impact on the ability to induce or maintain an immune response to a mycobacterial infection. The pathophysiologic mechanism for this increased risk of infection in patients with psoriasis is poorly understood. It is unclear what role if any IL-23 inhibition could contribute to this process. An overview of these cases with dose, time of onset, risk factors outcome etc. has been provided for further review. A detailed review of the individual events of serious pneumonia, cellulitis, osteomyelitis, sepsis, and herpes zoster demonstrates one or more predisposing risk factors in the majority of cases. No clear trends were identified and in the majority of cases, no recurrence of infection despite continued treatment with risankizumab. The risk of infection is greatest in the first 9 months of treatment with an overall trend towards a decrease in serious infections over 1 year of treatment. 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.

Section 4.8 includes additional wording regarding infections. Information on serious infections has also been included in section 4.8 of the SmPC**.**

Section 4.4 also includes a warning that patients with a chronic infection or known risk of infection or a history of recurrent infection who develop signs or symptoms of clinically important chronic or acute serious infection should be advised to seek medical advice and should be closely monitored. A further statement in section 4.4 recommends that treatment with risankizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated and if a patients develops an infection on treatment and is not responding to standard therapy for the infection, the patient should be closely monitored and risankizumab should not be administered until the infection resolves.

Based on the mechanism of action of risankizumab, the clinical findings in this application and previous experiences of similar immune-modulating biological medicinal agents, Serious Infections is included as an important potential risk in the RMP. This is endorsed by the CHMP/PRAC.

There was an increase in fungal infections reported in risankizumab treated patients compared to placebo and ustekinumab at 16 and 52 weeks. Overall exposure adjusted rates of fungal infection in patients treated with risankizumab 150mg declined slight over time ((5.2 E/100 PY) at 16 weeks compared with 3.9 E/ 100 PY overall. Tinea fungal infections accounted for some of this increased reporting rate of fungal infections reported in the risankizumab groups across all analyses including cases of tinea cruris, tinea manum tinea pedis, body tinea, tinea versicolour, and fungal skin infection and onychomycosis. These infections were generally mild to moderate in severity responsive to treatment and did not require treatment discontinuation. Tinea infections (tinea pedis, tinea cruris, body tinea, tinea versicolour, tinea manum) are included in the proposed SmPC as ADRs. Onychomycosis (tinea unguium infections) has also been included as an ADR in section 4.8.

There was also a significant clustering of reports of oral, oesophageal, cutaneous candidiasis and vulvovaginal candidiasis following treatment with risankizumab over the longer term. Oral and oesophageal candidiasis are captured both as fungal infections and opportunistic infections. These events did not result in discontinuation of study drug and were not identified as cases of serious, systemic fungal infections in the studies however Candida infections could be expected following treatment with risankizumab due to its disruption of the IL23/IL17 axis. Candida infections have been further discussed by the applicant. It is suggested that selective blockade of the IL23-specific p19 subunit with respect to distal blockade of IL-17A or its receptor protects against the development of candida infections. This is a hypothesis rather than an established fact. Although Candida infections are the second commonest group of fungal infections after tinea infections reported in the risankizumab safety database, there was no significant increased reporting of candida infection compared to placebo in the Primary Safety Pool .It is agreed that candida infections can be omitted from section 4.8 of the SmPC. Increased Candida colonization has been confirmed in subjects with psoriasis. (Pietrzak 2018). 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 in future PSURs.

Although Herpes Zoster infections were low overall (<1% risankizumab group treated subjects across any of the 3 analyses) 7 cases including 2 that were considered to be treatment related were reported in the original clinical safety summary. Cases of Herpes zoster associated with risankizumab were further discussed by the applicant. The number of reports of herpes zoster increased from 7 to 14 with inclusion of patients from the safety update. However, when adjusted for exposure the rate of infection increased from 0.3E/100PY to 0.4E/100PY. This suggests a slight trend towards increased rates of herpes zoster with additional exposure. This will be further monitored by the applicant in the post authorisation setting.

Across the Phase 3 psoriasis clinical studies, 72 subjects with latent tuberculosis (TB) were concurrently treated with risankizumab and appropriate TB prophylaxis during the studies. From the 31 subjects in Study M15-992 who had latent TB on screening and did not receive prophylaxis during the study, none developed active TB during the follow-up. Six cases of latent TB (0.4%: 0.4/100PY) were reported over 77 weeks exposure to risankizumab 150mg.Overall 8 subjects in the All Risankizumab group (all doses) reported latent TB but had no clinical symptoms. There continued to be no cases of active tuberculosis (TB) among risankizumab-treated subjects in this SUR, including no reactivation of TB in subjects diagnosed with latent TB.

The SmPC states that risankizumab must not be given to patients with active TB and recommends that patients with latent TB should be considered for anti-TB therapy prior to initiating risankizumab. This warning has been revised to include the warning that patients TB status should be evaluated prior to starting treatment and should be monitored for signs and symptoms of active TB during and after treatment.

The rates of injection site reactions were higher than placebo (1.5% vs. 1.0%, respectively), but lower than with ustekinumab (3.8%) or adalimumab (5.6%). In the All Risankizumab Psoriasis Analysis Set the ISR reporting rate remained low at 3.1% compared with 3.4% in the SUR. Injection site erythema was the commonest adverse event. Injection site reactions (injection site bruising, erythema, haematoma, haemorrhage, irritation, pain, pruritus, reaction, and swelling) are included as common side effects in section 4.8 of the SmPC. In the Primary Safety Pool and the All Risankizumab Psoriasis Analysis Set, the incidence of injection site reactions was numerically higher among antidrug antibody positive than the antidrug antibody negative subjects. The incidence of injection site reactions is numerically higher in the ADA-positive than the ADA-negative groups in both the Primary Safety Pool (2.7% vs. 1.3%) and the All Risankizumab Psoriasis Population (5.0% vs 3.3%). Although anti-drug antibodies with a significant ($\geq$ 128) titer were rarely (~1% of treated patients) occurring, most of these patients were NAb positive, and the occurrence of these higher titer antibodies apparently did have a negative impact on clinical response.

Increase rates of ISRs were seen at 16 weeks and over longer term treatment in ADA positive subjects. This has been reflected in section 4.8.

In the primary safety analysis hepatic events were more frequently reported for placebo than for the risankizumab 150mg treatment groups. Although there was no overall signal of more potential for hepatotoxicity in risankizumab patients compared to placebo or comparator treatment over the short to medium term, the incidence of 3 cases of possible drug induced liver injury following treatment with risankizumab: 2 cases following treatment with 150mg risankizumab for psoriasis and 1 case following treatment with risankizumab 150mg for psoriatic arthritis. Both cases in the psoriasis studies occurred within 30 days of treatment with risankizumab. Both were confounded by underlying medical conditions and concomitant medications however both cases case of liver injury were considered to be related to study drug by the investigator. One case in the Phase 2 psoriatic arthritis study met the laboratory criteria for Hy's law 56 days after the last dose of study drug. This case was also confounded by underlying medical conditions and concomitant medications. The events were reported resolved at the end of the study. This case was considered to be related to study drug by the investigator. This was the only one of the 3 cases associated with a high rate of combined elevations in hepatic transaminases and serum bilirubin. The MAH argues that given the presence of multiple confounders, the case does not meet the criteria for a Hy's Law case. The fact that the events occurred almost 2 months after receipt of study drug does suggest that treatment with risankizumab may have been unlikely to have played a role in the aetiology of this event. Severe cases of raised LFTs (4 cases of raised AST, 3 cases of raised ALT and 1 case raised LFT) were also reported, only one of which resulted in discontinuation of study medication. Patients with hepatic impairment were not excluded from the studies. PK of risankizumab was not evaluated in patients with hepatic impairment. An overview of safety in patients with hepatic impairment has been provided by the applicant including a review of hepatic events from the 7 month safety extension period covered by the SUR. Overall (up to 77 weeks exposure) AEs were reported in 62 subjects (3.9%) (5.9/100PY) treated with risankizumab 150mg compared with 112 of subjects (4.5%) (5.4E/100PY) in the SUR. In the SUR an additional two subjects are reported as having had serious hepatic AEs. However only one report is detailed. This patient (54year old white female) reported autoimmune hepatitis approximately 1yr after starting risankizumab. Details of the second case should be provided for review. Two additional cases of AST values 10-20 times ULN were reported. One additional subject met the criteria for Hy's law. This was attributed to liver congestion secondary to CHF. This patient subsequently died from CHF.

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 term, the incidence of 3 significant hepatobiliary SAEs leading to discontinuation of study drug is a concern. There was no preclinical signal for hepatotoxicity and neither has it been identified as risk with other similar type agents. There is no clear mechanistic basis for hepatoxicity associated with risankizumab. Currently no warnings in SmPC regarding hepatotoxic potential or need for monitoring of hepatic enzymes are required. The CHMP agrees that there is insufficient evidence to include hepatoxicity including drug induced hepatotoxicity as a potential risk in the RMP.

MACE events were more commonly reported in the placebo group compared with risankizumab at 16 weeks. No MACE events were reported for adalimumab and ustekinumab in the initial 16-week analysis. The overall MACE event rate (0.5 E/100PY) was low and was shown by the applicant to be in the range of MACE rates reported for ustekinumab, ixekizumab, secukinumab, brodalumab, and guselkumab at the time of their initial submissions. The treatment-emergent MACE event rate remained low at 0.4E/100PY in the SUR. Although the overall MACE event rate is low, after adjusting for exposure, there was a trend towards increased numbers of MACE, and other CV events with exposure to risankizumab over the longer term. Significant cardiovascular events were also more common following treatment with risankizumab

compared to ustekinumab over 52 weeks. However, rates of MACE and other CV never exceeded event rates reported for placebo at 16 weeks.

MACE is included as an identified potential risk in the RMP. A review of exposure-adjusted event rates of long-term data for MACE including a cluster of 5 adjudicated CV deaths) , Extended MACE and Other CV AE categories did not show increase over time in either CV event category. Event rates are comparable with short term event rates in RZB clinical studies as well as with CV event rates observed for psoriasis patients not undergoing biological PSO therapy**. .** In the Primary Safety Pool, 3.7% of RZB patients exhibited systolic blood pressure values ≥ 160 mmHg and ≥ 20 mmHg increase from Baseline until Week 16. Slightly higher frequencies (Risankizumab 150 mg subgroup: 6.2%, All RZB patients: 5.5%) were observed in All Risankizumab PSO Analysis Set.

Threshold for clinically relevant elevated blood pressure was based by Applicant on CTCAE Grade 3 hypertension definition: systolic BP >= 160mmHg or diastolic BP >=100mmHg, but for the latter 105mmHg was used as potentially clinically significant value.

Threshold for potentially clinically significant increase of > 20mmHg for systolic and >15 mmHg for diastolic blood pressure was clarified and finally accepted.

Risankizumab did not appear to have any clinically significant effects on the other cardiovascular functions (heart rate, or QT-interval).

When comparing risankizumab to ustekinumab at 52 weeks, the exposure adjusted incidence rates of malignancies appear similar, with 0.5 events per 100 PY for each treatment arm. The overall exposure adjusted event rate in patients treated with risankizumab 150mg was higher at 1.5E/100PY. The overall event rate for NMSC through Week 76 was 0.9E/100 PY in the risankizumab 150mg treated group. Corresponding event rates for malignancies other than NMSC through Week 76 were 0.6E/100 PY. The overall event rate (1.5E/100PY) was slightly higher than the range (0.81 – 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 applicant. The malignancy event rate (1.4E/100PY) 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 to evaluate safety risks, including malignancies. This is endorsed.

No association between hypersensitivity and treatment-emergent anti-drug antibodies was established. However, a warning regarding discontinuation of treatment if a serious hypersensitivity reaction occurs should be included in section 4.4. The applicant has adequately justified the omission of the ADR Hypersensitivity reaction (dermatitis contact, eczema, dermatitis, urticaria, and rash) from section 4.8. Serious hypersensitivity reactions is included as an identified potential risk in the RMP as monoclonal antibody products carry a theoretical risk of immune reactions against the small nonhuman part of the antibody. This is endorsed.

The overall rates of depression and depression related events in risankizumab treated patients were low (1.2 E/100 PY). Two subjects had a depression related SAE. None of the depression events led to discontinuation of study drug. There were no completed suicides in the risankizumab treated population. One subject had a self-injurious ideation AE that was not serious and 1 subject had a suicide attempt that was serious. Both events of SIB were in subjects with multiple confounding factors. The applicant has indicated that the SIB event rate (0.1 E/100 PY) is comparable to other recent clinical development programs (guselkumab 0.10/100 subject-yrs., secukinumab, 0.06/100 subject-yrs.; ixekizumab,

0.14/100 subject yrs.). There is no current evidence of causality of any of the SIB events with risankizumab. The CHMP agrees that there is insufficient evidence to include SIB as a potential risk in the RMP.

Retreatment Analysis Set

No new safety concerns were identified in patients withdrawn from treatment following improvement in their disease who then relapsed, and were retreated with risankizumab or in subjects who were switched from Adalimumab to Risankizumab.

On the basis of the information provided by the applicant the safety profile for the population who did not receive a loading dose is more favourable than the population who did receive a loading dose. Of the 899 subjects randomized to risankizumab 150 mg with loading Dose, 669 (74.4%) subjects had at least 1 AE. Three subjects died. Sixty-six (7.3%) subjects had an SAE and 19 (2.1%) subjects discontinued study drug due to an AE. whereas of the 191 subjects who didn't receive a loading dose, 132 (69.1%) subjects had at least 1 AE. No subjects died. Seven (3.7%) subjects had an SAE, and 2 (1.0%) subjects discontinued due to an AE. As outlined in the efficacy review, there is an increased benefit with the loading dose. As the differences in safety reporting is most likely due to methodological differences in how the data was collected rather than any real difference in safety profile between these two cohorts. These differential safety findings are not considered to impact on the R/B profile. Adverse Drug reactions

Estimates of the adverse drug reactions were based on safety data from the primary safety pool, complementing it with findings of significant adverse reactions observed throughout the studies. Events with longer latency and rare events were also evaluated this approach is acceptable. The AEs, considered by the applicant to be adverse drug reactions (ADRs): upper respiratory infections, headache, fatigue, injection site reactions, tinea infections, and folliculitis are acceptable.

Cough and pruritus occurred at a rate of $\geq$ 1% of subjects in the risankizumab group with a higher rate than the placebo group during the 16-week controlled period of pooled studies. Pruritus is included in the footnote 'e' for injection site reactions in section 4.8. However, the reports of pruritus were not specifically related to injection site reactions. Pruritus should be moved to the main body of the table. Cough was excluded from section 4.8 on the basis that it was an uncommon nonspecific event with no clear mechanistic basis. This is accepted by CHMP.

Laboratory findings

For haematology, mean changes from Baseline with risankizumab treatment groups were small and were not considered to be clinically meaningful. Rates were comparable to adalimumab and ustekinumab with no significant differences to placebo at 16 weeks. Following longer term exposure CTC toxicity grade 3 was noted for decreased Hb 1 case, platelets 1 case , leucocytes 4 cases, lymphocytes 6 cases) Grade 4 CTC toxicity values were observed for neutrophils decreased and lymphocytes decreased in 1 subject each. Although neutropenia is a potential risk, due the impact of blockade of IL23 / IL17 on innate immunity and neutrophil biology the number of reports of neutropenia is low (0.3%). There is no evidence of a clinically relevant impact on haematology values.

The mean changes from baseline with risankizumab treatment groups for clinical chemistry values, were small and were not generally considered to be clinically meaningful. Rates were comparable to adalimumab and ustekinumab with no significant differences to placebo at 16 weeks.

The most common CTC grade $\geq$3 clinical chemistry abnormalities over long term exposure in the risankizumab group were elevations in glucose, and triglyceride elevations, which occurred in 4.2%, and 4.7%, respectively, of subjects in the risankizumab treated group. Increased levels of triglycerides CTC

Grade ≥ 3 (>5.7mmol) were recorded in 89 subjects and 13 had readings >11.4 mmol/L. A similar picture was seen in the SUR.

66 patients treated with risankizumab 150mg had CTC Grade ≥ 3 blood glucose >13.9 mmol/L. No long term controlled data (i.e. ustekinumab) is presented for clinical chemistry values. Of note 3 cases of severe diabetes mellitus were reported over the same long-term exposure period. The high percentage of patients treated with risankizumab 150mg who had CTC Grade ≥ 3 blood glucose >13.9 mmol/L is for the main part explained by the high prevalence of diabetes mellitus in the overall psoriasis patient population. However, it noted that only 54 of the 66 patient with grade 3 blood glucose had a diagnosis of diabetes mellitus. It is unclear where the other 12 cases were reported. This should be clarified by the applicant. It is noteworthy however that over 52 weeks there was a small increase from baseline in blood glucose in the risankizumab 150 mg arm and in the ustekinumab arms (0.2 mmol/L mean vs. 0.3 mmol/L respectively). The clinical significance of this finding is unclear. The applicant has committed to continuing to monitor blood glucose in all ongoing and planned studies, to evaluate the impact of risankizumab on blood glucose levels.

There were 8 reports (0.6%) of creatine kinase increased including 3 reports (0.2%) of a CTC AE toxicity grade 4 at 16 weeks. The overall percentage (0.9%) including the percentage of grade 4 events (0.6%) increased over longer term exposure. The applicants' analysis of the Grade 3 and Grade 4 increases in creatine kinase for risankizumab 150 mg over shorter and longer term treatment indicates that an association between creatine kinase increases and risankizumab treatment is unlikely. There were 3 reports of a CTC AE toxicity grade 4 chemistry abnormality (elevated AST n= 2 and ALT n=1). All of which occurred within 16 weeks of starting treatment. (See discussion on Liver Function test values below) At 16 weeks the proportions of subjects with potentially clinically important changes in ALT, AST, ALP, and bilirubin values in the risankizumab 150mg 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 150mg group were recorded in <3% of patients. AST and ALT elevation ≥ 5 ULN were reported in <1% of subjects. There were 2 subjects with ALT elevation of > 20 × ULN.. Subjects also had AST elevation of > 20 × ULN) associated with a drug induced liver injury (SAE) this case is further discussed as an adverse event of special interest. A subject who was treated with 90 mg risankizumab had a history of fatty liver. The elevation resolved after 2 weeks. This was not considered to be an SAE.

Special populations

Treatment-emergent AEs were slightly higher in females compared with males. The proportions of subjects with SAEs, or who discontinued due to an AE in the risankizumab group was generally similar among men and women over short and longer term treatment apart from reports of deaths. Five deaths occurred in male however, this may be accounted for by males being the majority (70% in All Risankizumab – Psoriasis) of the subject population.

The overall rates of AE experienced in subjects ≥ 65 years of age and are comparable to the overall population however higher rates of SAEs, AEs leading to discontinuation, and severe AEs may relate as suggested by the applicant to increasing comorbidities in the elderly population. However, rates of SAEs, AEs leading to discontinuation, and severe AEs were further discussed by the applicant. The applicant's response has not provided complete reassurance regarding the safety of risankizumab in this population as the dataset is so limited particularly in patients over 75. A statement to the effect that safety data in older patients is limited has been included in section 4.8 of the SmPC. .

Impact of Baseline static Physician's Global Assessment (sPGA; 3, 4), and body weight (≤ 100 kg, ≥ 100 kg) had no discernible impact on the overall safety profile of risankizumab .

Despite the requirement that women of childbearing potential were required to use highly effective methods of birth control in the studies 17 women became pregnant. The current wording in section 4.6 is in line with the recommendations of the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation. The SmPC advises that it is preferable to avoid the use of risankizumab in pregnancy. However Psoriasis is common in women of childbearing age, with many women requiring ongoing therapy to maintain remission and improve quality of life. Therefore, pregnancy and the use of biologics in lactation may be frequently encountered in clinical practice. 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.

The SmPC statement on breastfeeding has also been revised to reflect the fact that although currently it is unknown whether risankizumab is excreted in human milk it is known that some Human IgGs are excreted in breast milk during the first few days after birth therefore a risk to the breast-fed infant cannot be excluded . Any decision to discontinue/abstain from risankizumab therapy should take into consideration the benefit of breast-feeding to the child and the benefit of risankizumab therapy to the woman.

Immunogenicity

The incidence of treatment emergent ADAs (19%) at 16 weeks increased up to 24% after 52 weeks. A total of 9% and 14 % of patients treated with risankizumab at the recommended dosing regimen developed neutralizing antibodies to risankizumab at 16 and 52 Weeks respectively. The overall incidence of ADA and NAB appears to further increase following stopping then retreating with risankizumab. Despite the high levels of ADA, no subject exposed to risankizumab in the psoriasis studies experienced anaphylactic reactions or serum sickness-like reactions however 2 subjects in the psoriatic arthritis studies did experience anaphylactic reactions.

The incidence of injection site reactions was higher among ADA positive (2.7% and 5%) than the ADA negative (1.3% and 3.3%) at 16 and 52 weeks respectively. The Applicant provided additional data from Study M15-992 up to 104 weeks. The overall incidence of treatment emergent ADAs and NABs 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 incidence of injection site reactions are numerically higher in the ADA-positive than the ADA-negative groups at 16 and 52 weeks. The wording of section 4.8 has been revised accordingly. Persistent relatively high levels of antibodies were attributed to the sensitivity of the assay. Rates of ISRs and hypersensitivity reactions were low. Addition of immunogenicity as an important potential risk in the RMP is not currently warranted.

2.6.2. Conclusions on clinical safety

Data from 2234 patients of whom 1590 were initially treated with risankizumab 150mg s up to 77 weeks have been used to characterise the safety profile of risankizumab. This has been supplemented by a safety update report including data from an additional 237 subjects representing an additional 1185.0 PY of exposure for a total of 3351.6 PY of exposure. The overall adverse event rates of risankizumab in the pooled data tended to be more favourable to the active comparators adalimumab and ustekinumab. In the 16-week period after initial treatment, the exposure adjusted event rate for overall adverse events was higher than placebo but lower than ustekinumab and adalimumab.

SAEs and severe adverse events and AEs leading to discontinuation of study drug were reported less frequently for risankizumab compared to placebo, adalimumab and ustekinumab treatment groups suggesting that in the initial treatment period risankizumab has a more favourable safety profile however this was not consistent across all SOCs e.g. infections were more frequently reported following treatment with risankizumab compared with ustekinumab.

Over the longer term (52 weeks) the safety profiles of risankizumab treated patients reported slightly less AEs and SAEs but had more severe AEs than ustekinumab. Exposure-adjusted TEAE rates for risankizumab 150mg calculated as events/100 PY were similar across the three safety analyses groups suggesting that there was no increase in the event rate for AEs with longer exposure to risankizumab. Overall risankizumab 150mg was well tolerated with discontinuation due to adverse events <2%. Common adverse events were predominately mild (>97%). Viral URTI and URTI, arthralgia and headache were the commonest adverse events. Local tolerability was better compared to adalimumab and ustekinumab.

Although serious infections were reported in <1% of risankizumab treated patients at 16 weeks and exposure adjusted rates of serious infections were comparable between risankizumab analyses at 16, 52 and 77 weeks, and over the additional 7month safety review. Increased mucocutaneous fungal infections (tinea and candidiasis) were noted following treatment with risankizumab particularly over longer term treatment. This is stated in he SmPC.

Three cases of drug induced liver injury were experienced in the patients treated with risankizumab. Although all of these cases were confounded, all three cases resulted in study drug discontinuation and were considered to be related to study drug by the investigator. There is insufficient data to include hepatotoxicity as a potential risk in the RMP. Cases of hepatoxicity will be monitored using routine pharmacovigilance.

The overall malignancy rate in subjects exposed to risankizumab 150mg was slightly higher than those reported in the clinical development program for similar type agents. The effect of risankizumab on blood glucose homeostasis will be further characterised in the post authorisation setting.

Immunogenicity over 104 weeks has been characterised.

2.7. Risk Management Plan

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
MACE	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all postmarketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Long-Term Extension Study
Serious infections	Routine risk minimization measures: Product labeling (SmPC Section 4.3, Contraindications and Section 4.4, Special warnings and precautions for use) Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all postmarketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Long-Term Extension Study
Malignancies	Routine risk minimization measures:	Pharmacovigilance activities beyond

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	adverse reaction reporting and signal detection: • Biweekly line listing review of all postmarketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Long-Term Extension Study
Serious hypersensitivity reactions	Routine risk minimization measures: SmPC Section 4.3 indicates contraindication if known hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1. SmPC Section 4.4 states if a serious hypersensitivity reaction occurs, administration of risankizumab should be discontinued immediately and appropriate therapy initiated. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all postmarketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Long-Term Extension Study
Using during pregnancy and lactation	Routine risk minimization measures: SmPC Section 4.6 Fertility, pregnancy and lactation	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	postmarketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: Pregnancy Exposure and Outcomes for Women Treated with Risankizumab
Use in patients with chronic HBV or chronic HCV infection	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all postmarketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: None
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	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: • Biweekly line listing review of all postmarketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials. • Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database. • Periodic reports to agencies

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
skin or in situ carcinoma of uterine cervix		(e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines. Additional pharmacovigilance activities: Long-Term Prospective Cohort Study in Real World Setting
Long-term safety in patients with moderate to severe plaque psoriasis	Routine risk minimization measures: None. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	• Long-Term Prospective Cohort Study in Real World Setting • Risankizumab Long-Term Extension Study

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD).The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that risankizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers risankizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the*

readability of the label and package leaflet of medicinal products for human use.

2.10.2. Quick Response (QR) code

A request to include a QR code in the labelling (outer carton) and package leaflet for the purpose of providing statutory and additional information (see below) on the medicinal product has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: link to a website (URL: www.skyrizi.eu) including the package leaflet (statutory information) in an interactive, more easily navigable format, and a video on how to safely inject Skyrizi (additional information). This video is based on section 7 of the package leaflet and aims to be an additional tool to support the patient.

The company was requested to confirm that during the life cycle of the product, the QR code would be amended as appropriate. The company confirmed and clarified that due to lead times of producing physical packs, elabelling websites such as the QR website will always be updated faster than the printed version of the Package Leaflet in the pack. On the Skyrizi QR website, a statement on the bottom of each page *'This page was last revised : [MM/YYYY]'* will inform about the last update.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Skyrizi (risankizumab) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1.1. Disease or condition

Psoriasis is a chronic debilitating immunologic disease characterized 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%.

Plaque psoriasis is the most common form, affecting approximately 80% to 90% of patients. In patients with plaque psoriasis, approximately 80% have mild to moderate disease, with 20% having moderate to severe disease.

The proposed indication is for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The goal of treatment is to control signs and symptoms of plaque psoriasis and improve quality of life for patients with this condition.

3.1.2. Available therapies and unmet medical need

Topical corticosteroids are commonly used for mild to moderate cases. Other topical medications include keratolytic agents, anthralin, coal tar, vitamin D analogs, and retinoids. For more widespread disease, phototherapy (ultraviolet B [UVB] or psoralen with ultraviolet A [PUVA]) is commonly used. Systemic therapy, including methotrexate (MTX), cyclosporine, synthetic retinoids, and fumaric acid are often effective in patients with moderate or severe disease. Due to the potential adverse side effects of systemic agents, these medications are generally administered in rotation to avoid long-term or cumulative toxicities.

Biological therapies have emerged as an alternative treatment option for patients with moderate to severe psoriasis in need of systemic therapy as detailed below.

Expression of tumour necrosis factor (TNF)-induced proteins in psoriatic plaques provided the rationale for the development of TNF-neutralizing therapies for psoriasis,20 and the anti-TNF agents etanercept, adalimumab, and infliximab are approved for the treatment of moderate to severe psoriasis.

Ustekinumab, a p40 IL 12/23 inhibitor, is approved for the treatment of moderate to severe psoriasis.

Recently more targeted biological therapies such as Guselkumab, an IL-23 inhibitor (p19 subunit of IL-23) and anti-IL-17 monoclonal antibodies such as brodalumab, ixekizumab, and secukinumab have been approved.

These more targeted therapies such as IL-17 and IL-12/23 inhibitors have added incremental clinical benefit. While there is not a large unmet need, newer more efficacious treatments compared to earlier approved biological therapies are welcome to improve clinical response and quality of life of plaque psoriasis patients.

3.1.3. Main clinical studies

The risankizumab psoriasis clinical development program designed to support the proposed indication included 4 pivotal Phase 3 studies of the dose and dosing regimen (risankizumab 150 mg subcutaneous [SC] injection at Weeks 0, 4, and every 12 weeks [q12w] thereafter) in adults who had stable moderate to severe chronic plaque psoriasis ≥ 6 months (with or without psoriatic arthritis), defined as body surface area (BSA) involvement ≥ 10%; Psoriasis Area and Severity Index (PASI) score ≥ 12; Static Physician Global Assessment (sPGA) ≥ 3.

Studies M15-995 (1311.28) (UltIMMa-2), M16-008 (1311.3) (UltIMMa-1): Multicentre, randomized, double-blind, placebo- and active-controlled studies that compared the efficacy and safety of risankizumab treatment with placebo and ustekinumab treatment.

Study M15-992 (1311.4) (IMMhance): A multicentre, randomized, double blind study that compared the efficacy and safety of risankizumab treatment with placebo, evaluated the effects of continuous risankizumab compared with withdrawal in risankizumab responders, and evaluated re-treatment of subjects who experienced relapse. This study is still ongoing (interim results provided).

Study M16-010 (1311.30) (IMMvent): A multicentre, randomized, double blind study that compared the efficacy and safety of risankizumab with adalimumab and evaluated switching from adalimumab to risankizumab for adalimumab non-responders and those with inadequate response to adalimumab.

(Study M15-997) Long-term efficacy and safety of risankizumab. This study is ongoing; the data cut-off date was 01 September 2017.

The pivotal studies were supported by a Phase 2 study dose finding study (Study 1311.2) and its OLE (Study M16-009 [1311.13]), and a Phase 1 study (Study 1311.1).

The endpoints chosen by the company are agreed and are of clinical relevance, furthermore they are in line with relevant guidelines and previous therapies which have been authorised.

The co primary endpoints PASI 90 responses and IGA0-1 were agreed as the primary endpoints as were the secondary endpoints which examined for longer term efficacy, relative efficacy and symptomatic endpoints QoL measurements.

3.2. Favourable effects

A total of 2109 subjects were randomized in the Phase 3 studies of those subjects, 1306 were randomized to risankizumab. An additional 375 subjects switched to risankizumab in later parts of the pivotal studies, and 348 subjects switched to risankizumab in the open-label extension Study M15-997.

Demographic characteristics and disease severity were balanced across treatment groups and studies and were consistent with those seen in other recent trials of biologics in plaque psoriasis.

The co-primary efficacy endpoints in the first period of Phase 3 pivotal studies (Part A, Baseline to Week 16), PASI 90 and sPGA of clear or almost clear at Week 16, were in agreement with CHMP scientific advice and regulatory advice received prior to starting the Phase 3 program.

Risankizumab was superior to placebo as demonstrated by statistically significant differences between groups in the proportions of subjects who achieved PASI 90 (73.2 % -75.3% vs 2.0-4.9% risankizumab versus placebo respectively) and sPGA of clear or almost clear (83.5% to 87.8% vs 5.1 to 7.8% risankizumab versus placebo respectively- both $p < 0.001$ studies M15-995, M16-008, M15-992).

Risankizumab was superior to Adalimumab for both co primary endpoints at week 16 PASI 90 (72.4% vs 47.4 % Risankizumab vs Adalimumab resp) and s PGA (83.7% vs 60.2% Risankizumab vs Adalimumab resp. both $p < 0.001$ study M16-010).

Consistent effects were demonstrated for the co primary endpoints across the four studies.

Key secondary endpoints examined for the co primary endpoints at week 52 this showed consistent effects with week 16 results and achieved slightly higher efficacy: s PGA (83.3% – 86.2%) and PASI 90 (91.5%-91.8%) at week 52.

Higher efficacy such as PASI 100 and s PGA of clear at weeks 16 and at week 52 (studies M15-995, M16-008) were also demonstrated, as superiority was achieved with risankizumab compared to either placebo or Ustekinumab at both week 16 and 52 for sPGA clear (average diff vs Ustekinumab + 45.6% at week 16, + 32.9% at week 52) PASI 100 (average diff Ustekinumab + 25.2 % week 16, + 32.25% at week 52).

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 psoriatic arthritis, 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 at Week 16 In addition, consistent response rates were shown in PASI 90 and sPGA of clear or almost clear regardless of anti-drug antibody status and NAb status.

Risankizumab was also superior to placebo for improving the extent and severity of nail, palmoplantar, and scalp psoriasis, as demonstrated by statistically significant differences as the secondary endpoint ($P < 0.001$ for each comparison) between treatment groups in favour of risankizumab in mean changes from Baseline in NAPSI (-10.6 ls mean vs placebo at week 16), PPASI (-4.35 ls mean vs placebo at week 16), and PSSI (-14.4 ls mean vs placebo at week 16) in the Placebo- Controlled Population. Additionally, superiority to ustekinumab for improving the extent and severity of nail and scalp psoriasis compared with ustekinumab (both $p < 0.0010$) however but not for palmoplantar psoriasis.

Switching to risankizumab for subjects who had inadequate initial response to adalimumab (PASI 50 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 0/1) and PSSD (clinically meaningful change in both symptom and sign scores) were observed.

Two-thirds of subjects in the risankizumab group achieved DLQI of 0 or 1 (psoriasis had no impact on subject's quality of life) at Week 16 compared with 5% of subjects who received placebo. At Week 52, over 70% of subjects who were randomized to receive risankizumab 150 mg at Baseline reported no impact on their quality of life from psoriasis, and approximately 56% of subjects who received risankizumab in Studies M16-008 and M15-995 reported no itch, pain, burning, or redness.

Risankizumab also showed meaningful impact on patient-reported psoriasis symptoms (itch, pain, redness and burning), as measured by the Psoriasis Symptom Score (PSS), and quality of life. Almost one-third of subjects in the risankizumab group achieved a PSS score of 0 at Week 16 compared with 1% of subjects in the placebo group.

Overall incidence of antidrug antibodies was 19% across the clinical programme with 8% incidence of neutralising antibodies at 16 weeks. This was increased at week 52 to ADA 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.

3.3. Uncertainties and limitations about favourable effects

The majority of subjects who were randomized to risankizumab were male (69.5%) and white (78.1%) subjects had a median baseline PASI score of 17.80 and a median BSA of 20.0% and were mostly middle aged. Therefore other races female population and elderly were under represented however there is no indication to date that other races would respond differently to the overall population.

Overall very high PASI 90 and s PGA 0/1 responses were demonstrated however not all patients respond (14% s PGA and < 20% PASI 90) while subgroup analyses did not identify a single variable of concern and statistically significant and clinically relevant differences from placebo were seen, it was demonstrated that the effects s PGA 0/1 were lower with high body weight (patients < 106 kg 81.9% vs patients > 128.2 kgs 69.7 % difference from placebo). Also in patients with high ADA titres, although antibody responses were not shown to have affected the efficacy results the number of patients who developed antibodies is very low and the duration is limited, however evidence to date is favourable.

Although the patient numbers were low it was observed that patients with high ADA titres ≥ 128 did not achieve the same favourable results as the patients with ADA titres < 128.

It is unclear what results would be achieved in patients with body very high body weight and high ADA responses, Nevertheless a slight loss of efficacy was observed in patients with more than 130 kgs compared with those <130 kgs. However no dose adjustment is considered necessary.

Overall the majority of patients had moderate disease as baseline sPGA score was severe in 19.3% of subjects. Although it is agreed that the indication is for moderate and severe plaque psoriasis the analysis included both populations support the effects in each subgroup separately.

It does not appear that patients were allowed rescue therapy during the programme however if patients required use, such as moderate to high potency topical steroids or systemic steroids whether any additional benefit would have been demonstrated or indeed the safety of this combination is unclear.

In Study M15-992 patients who were randomised to withdrawal or continued treatment, a waning of efficacy was noted as early as Week 40, after missing only one dose, with a statistically significantly greater proportion of subjects on continuous risankizumab treatment maintaining sPGA 0/1 compared to those who were randomised to placebo at Week 40 (91.9% versus 81.8%, $P < 0.01$). If a dose was missed it is advised to take the dose immediately and resume dosing regimen at the regular time.

For PASI responses the effect size between risankizumab and placebo was 33.1% for PASI 90 and 33.7% for PASI 100, and the median time to loss of PASI 100 was shorter, at 113 days (HR 0.286, $P < 0.001$), with a 25th percentile of 57 days. While there appears to be still a high maintenance of effects following withdrawal there is a decline noted in patients some of whom may have failed other treatments, it is not known whether patients who achieve sustained clinical remission could be managed with lower of less frequent dosing, the applicant is encouraged to further explore this in the post authorisation setting.

3.4. Unfavourable effects

With over 2,471 subjects with a total of 3351.6 PY of treatment duration the ICH E1 safety exposure requirements of >1500 patients exposed, 300 to 600 for 6 months, > 100 for 1 year met however less than 6.6%% were exposed for two years or more.

Eighty percent of participants were White, 3% Black or African American. Approx. one third of participants were female. Ten percent of subjects were between 65 and 74 years of age.

In the first 16 weeks of treatment, 22.1% of subjects in the risankizumab 150 mg group reported infection AEs (90.8 E/100 PY) compared to 14.7% of subjects in the placebo group (56.5 E/100 PY), 20.9% of subjects in the ustekinumab group (87.0 E/100PY), and 24.3% of subjects in the adalimumab group (104.2E/100 PY) based on the Infections and infestations SOC. After 52 weeks of exposure, 44.8% of subjects treated with risankizumab (73.9 E/100 PY) compared with 52.3% of subjects treated with ustekinumab (90.1 E/100 PY) reported infection AEs. Over the entire psoriasis program, 40.8% of subjects in the All Risankizumab group reported infection AEs (75.5 E/100 PY). The most commonly reported infections viral upper respiratory tract infection, upper respiratory tract infection, urinary tract infection, and sinusitis The majority of infections (97.8%) were non serious and mild to moderate (Grade 1 or 2) in severity most of which did not necessitate treatment discontinuation.

At 16 weeks five (0.4%) subjects in the risankizumab 150mg group experienced serious infections (1.7 E/100 PY) compared to (0.3%) of the subjects in the placebo group (1.1 E/100 PY). After 52 weeks in the ustekinumab controlled analysis eight (1.3%) subjects in the risankizumab group experienced serious infections (1.8 E/100 PY) compared to 4(2.0%) subjects in the ustekinumab group (2.0E/100 PY). Over the entire psoriasis program (all doses), serious infections (using the Infections and infestations SOC) were reported in 29 (1.3%) subjects treated with risankizumab (1.8E/100 PY (95% CI 1.27, 2.45) (1.5E/100PY in the SUR)). Serious infections in the risankizumab population (all doses) reported in ≥ 3 subjects included sepsis (7 cases), cellulitis (5 cases), and pneumonia (4 cases). There were 2 serious cases each of osteomyelitis and herpes zoster. One case each of pneumonia and sepsis resulted in discontinuation of study medication. Erysipelas was also reported in ≥ 3 subjects this SUR.

The overall rate of fungal infections in the risankizumab 150 mg group was higher than in the placebo and ustekinumab groups (over short and long term exposure) and lower than in the adalimumab group. Over 16 weeks 1.5% subjects in the risankizumab 150 mg group experienced fungal infections (5.2 E/100 PY) compared to 0.3% of the subjects in the placebo group (1.1 E/100PY), 0.8% subjects in the ustekinumab group (2.6 E/100 PY), and 2.0% subjects in the adalimumab group (7.4 E/100 PY). Over 52 weeks 4.0% subjects in the risankizumab group experienced fungal infections (4.2 E/100 PY) compared to 1.0% subjects in the ustekinumab group (1.0 E/ 100 PY). Over the entire psoriasis program (risankizumab 150mg group) 3.5% of the risankizumab treated patients (3.9 E/100PY (95% CI 3.04, 4.99)) experienced

fungal infections. Mucocutaneous tinea and candida fungal infections accounted for this increased reporting rate of fungal infections Tinea infections reported in the risankizumab groups across all analyses including cases of tinea cruris, tinea manum tinea pedis, body tinea, tinea versicolour, and fungal skin infection and onychomycosis. These infections were generally mild to moderate in severity responsive to treatment and did not require treatment discontinuation. There was also a significant clustering of reports of oral, oesophageal, cutaneous candidiasis and vulvovaginal candidiasis following treatment with risankizumab over the longer term. Oral and oesophageal candidiasis are captured both as 'Fungal infections and opportunistic infections. Overall 5 cases of candida were reported as opportunistic infections. None of these events resulted in discontinuations in the studies and were not identified as cases of serious, systemic fungal infections. Candida infections were mild to moderate in severity and none led to treatment discontinuation.

At 16 weeks Grade 3 neutropenia was reported in one patient treated with risankizumab. Overall 4 subjects reported Grade 3 or 4 neutropenia, 2 of whom had a single excursion to Grade 3 followed by return to Baseline or close to Baseline (1 was described in the Primary Safety Pool above). The other 2 subjects had low neutrophil counts (Grade 3 or 4) prior to receipt of study drug and remained low through most of the study. None of the Grade 3 neutropenia was associated with severe or serious infections.

Eight subjects in the All Risankizumab group reported latent tuberculosis but had no clinical symptoms.

The incidence of treatment emergent ADAs (19%) at 16 weeks increased up to 24% after 52 weeks and remained stable at 27% over 104 weeks. A total of 9% , 14 % and 17% of patients treated with risankizumab at the recommended dosing regimen developed neutralizing antibodies to risankizumab at 16 ,and 104 52 Weeks respectively. The overall incidence of ADA and NAB appears to further increase following stopping then retreating with risankizumab. Despite the high levels of ADA, no subject exposed to risankizumab in the psoriasis studies experienced anaphylactic reactions or serum sickness-like reactions.

The incidence of hypersensitivity AEs in risankizumab treated patients was comparable to placebo and adalimumab groups but higher than the ustekinumab group over both short and longer term exposure, driven by higher rates of dermatitis contact, eczema, dermatitis, and urticaria. None of the hypersensitivity reactions were serious or led to discontinuation of study drug. Two cases of anaphylaxis have been reported in patients treated with risankizumab for Crohn's disease and Psoriatic arthritis.

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are recognized comorbidities for psoriasis patients, despite this the overall reporting of hepatic events in these studies was low. During the 16-week treatment period hepatic events were more frequently reported for placebo (7.6 E/100 PY) and the ustekinumab (9.2 E/100 PY) treated patients and less frequently for adalimumab (5.3 E/100 PY) compared to risankizumab 150mg treated patients (6.0 E/100 PY). Overall the hepatic event rate was 5.6 E/100 PY. Similarly, the incidence of serious and severe hepatic adverse events was low. However, it is noteworthy that three cases of possible drug induced liver injury were reported following treatment with risankizumab, 2 cases following treatment with 150mg risankizumab for psoriasis and 1 case following treatment with risankizumab for psoriatic arthritis. All three cases had significant confounding factors (liver disease, concomitant medications. All three were considered possibly related to study drug by the investigator. Study was discontinued in all three cases. The case following treatment with risankizumab for psoriatic arthritis met the biochemical criteria for a Hy's Law case; however, following clinical review, given the presence of multiple confounders, the applicant considers that case does not meet the criteria for a Hy's Law case. Four cases of raised LFTs were reported as severe. One additional patient met the criteria for HY's law in the safety report. This was attributed to liver congestion following CHF.

Injection site reactions following treatment with risankizumab150mg, were reported more frequently than with placebo (1.5% vs. 1.0%, respectively), but less frequently than with ustekinumab (3.8%) or

adalimumab (5.6%).The incidence of injection site reactions was higher among ADA positive (2.7% and 5%) than the ADA negative (1.3% and 3.3%) at 16 and 52 weeks respectively. Overall (3.1%) reported injection site reactions. None of the injection site reactions were considered severe or led to study discontinuation.

The overall malignancy event rate (All Risankizumab – Psoriasis Analysis Set) was 1.3% (1.5 E/100 PY (0.96, 2.19)) for subjects exposed to risankizumab 150mg. The majority of these were nonmelanoma skin cancers (0.9 E/100 PY). There were no reports of lymphoma or lung cancer. Rates of malignant tumours for patients treated with risankizumab 150mg were slightly higher than those reported in the ustekinumab, ixekizumab, secukinumab, guselkumab, and brodalumab clinical development programs (0.81 – 1.3 E/100 PY) (Centocor 2008, FDA 2016, CDER 2016a, van de Kerkhof 2016, CDER 2016b). One patient treated with risankizumab 150mg died from metastatic bowel cancer. This was not considered related to study drug.

Patients with moderate to severe psoriasis have been shown to have an increased risk of myocardial infarction, stroke and CV mortality. MACE, extended MACE, and other CV events were adjudicated by blinded external experts. The MACE rate in the risankizumab 150 mg group in the controlled portions of the studies (16 weeks of treatment) was 0.2 E/100 PY (1 case of CV death), compared to 1.1 E/100 PY in the placebo group. There were no MACE events in the comparator ustekinumab or adalimumab groups. One additional subject experienced an extended MACE and 2 subjects experienced CV events.

After 52 weeks of exposure, the MACE rate in the risankizumab group was 0.3 E/100 PY. Two (0.3%) subjects in the risankizumab group experienced a MACE. Two additional subjects experienced an extended MACE and 7 risankizumab-treated subjects experienced other CV events (1.3 E/100 PY). There were no MACE or other CV events reported in the ustekinumab comparator group.

The overall MACE event rate for subjects with psoriasis treated with risankizumab 150mg is 0.5 E/100PY). Four additional subjects experienced extended MACE, a further 13 subjects had other CV events. Four of 5 deaths in patients treated with risankizumab 150mg were adjudicated as treatment emergent CV deaths (one of these deaths was subsequently attributed to a drug overdose) and 2 other deaths that were classified as cause undetermined. Three of the deaths occurred in subjects with multiple cardiac risk factors and were likely to have had a cardiac cause. All of the deaths were considered by the Applicant to be unrelated to study treatment.

Five additional deaths were reported in the safety update report submitted during the procedure. (Preferred Terms of epileptic seizure, pancreatitis, cardiac arrest, cardiac failure, and death). This doubles the total number of deaths, bringing it to a total of 10 deaths, following treatment with risankizumab. Two and possibly a third death being adjudicated as cardiovascular deaths. All 10 deaths occurred in male patients.

Neuropsychiatric disorders are more frequent in patients with psoriasis. Depression as well as suicidal ideation and behaviour are more commonly reported in patients with psoriasis. Suicidal Ideation behaviour (SIB) has been identified as potential safety concern in other therapies that act on the same pathways in plaque psoriasis. Overall (All Risankizumab 150mg – Psoriasis Analysis Set), the depression event rate in the All Risankizumab group was 1.2 E/100 PY. Twenty (1.3%) subjects had a depression event, 16 of which were AEs of depression. Of the 16 subjects with depression, 2 subjects had an SAE. None of the depression events led to discontinuation of study drug. In this analysis set, the SIB event rate was also low (0.1 E/100 PY). There were no completed suicides in the risankizumab psoriasis clinical studies. One subject had a self-injurious ideation AE that was not serious and 1 subject had a suicide attempt that was serious. There were no discontinuations due to SIB AEs. Both events of SIB were in subjects with multiple confounding factors. The SIB event rate (0.1 E/100 PY) is comparable to the SIB rate in other recent clinical development programs (guselkumab 0.10/100 subject-yrs, secukinumab, 0.06/100 subject-yrs; ixekizumab, 0.14/100 subject yrs).

The overall rates of AE experienced in subjects ≥ 65 years of age and are comparable to the overall population however higher rates of SAEs, AEs leading to discontinuation, and severe AEs were reported in over 65 age group.

Overall 78.7% of women and 73.2% of men reported AEs. The proportions of subjects with SAEs, or who discontinued due to an AE in the risankizumab group was generally similar among men and women apart from reports of deaths.

3.5. Uncertainties and limitations about unfavourable effects

Although 7 months additional safety data has been submitted by the applicant long-term exposure to risankizumab (>18months) is limited. Only 6.6% were exposed for more than 2 years and only 3.4% exposed for more than 3 years in clinical trials. This extent of exposure is insufficient to fully characterize the unfavourable effects particularly those with a long induction period (malignancy) or those that might change with repeat exposure over time (ADA profile and immunological AEs). Long term data has been included as missing data in the RMP. Long term safety will be further characterised in the post authorisation setting.

The most frequently reported adverse events were infections. At 16 weeks exposure-adjusted infection AEs in the risankizumab treated population were higher than placebo and ustekinumab but lower than adalimumab. Over longer tem treatment, the exposure adjusted event rate decreased and was lower than the ustekinumab event rate at week 52. There was a slight increase up to 77 weeks of exposure but overall the exposure adjusted event rate for infections was stable over longer term exposure.

Although the overall rate of serious infection is low and remained stable across short and long-term exposure, there were(including reports from the SUR) 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. The extent to which disruption of the IL23 pathway and its impact on the risk for the development of serious bacterial infections will be further characterized in the post authorisation setting.

There was an increased reporting rate for fungal infections in risankizumab treated patients compared to placebo and ustekinumab (over 16 and 52 weeks). Tinea fungal infections accounted for some of this increased reporting rate of fungal infections reported in the risankizumab groups across all analyses. There was also a significant clustering of reports of oral, oesophageal, cutaneous candidiasis and vulvovaginal candidiasis following treatment with risankizumab over the longer term. Candida infections could be expected following treatment with risankizumab due to its disruption of the IL23 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 SAEs leading to discontinuation of study drug is a concern. Inclusion drug induced hepatotoxicity as a potential risk in the RMP is currently not warranted. Cases of hepatotoxicity will continue to be monitored in PSURs.

The incidence of treatment emergent ADAs was relatively high, 19% of subjects at 16 weeks developed ADAs increasing up to 24% after 52 weeks. A total of 9% and 14 % of patients treated with risankizumab at the recommended dosing regimen developed neutralizing antibodies to risankizumab at 16 and 52 Weeks respectively. The incidence of injection site reactions was numerically higher among antidrug antibody positive than the antidrug antibody negative subjects. Immunogenicity has a small but clinically relevant impact on injection-site reactions. This is included in section 4.8 of the SmPC. Inclusion of immunogenicity as a potential risk in the RMP is currently not warranted.

Although the overall MACE event rate is low (0.5E/100PY), after adjusting for exposure, there was a slight trend towards increased numbers of MACE, and other CV events with exposure to risankizumab over the longer term. At 16 weeks the reporting rate for MACE in the risankizumab 150 mg group was 0.2 E/100 PY compared with 0.3 E/100 PY at 52 weeks and 0.5E/100PY overall although the event rate never exceeded the event rate for placebo at 16 weeks (1.1E/100PY). Significant cardiovascular events were more common following treatment with risankizumab compared to ustekinumab at 16 and over 52 weeks. Four of five deaths initially reported for risankizumab were initially adjudicated as CV deaths. Three of the four patients who died had significant confounding CV history. The remaining death was attributed to an opioid drug overdose.

Overall the event rate of any malignant tumour (including nonmelanoma skin cancer [NMSC]) with risankizumab (all doses) was 1.3 E/100 PY and slightly higher at 1.5E/100PY for subjects treated with risankizumab 150mg only. This is slightly higher than the rates of malignant tumours reported in the ustekinumab, ixekizumab, secukinumab, guselkumab, and brodalumab clinical programs (0.81 – 1.3 E/100 patient-years).

The overall suicidal ideation and behaviour rate was low. Although suicidal ideation and behaviour have been included in the RMPs for other similar type products, there is insufficient data to support its inclusion as an important potential risk in the RMP for risankizumab.

3.6. Effects Table

Table 59: Effects Table for Risankizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.

Effect	Short Description	Unit	Risankizumab	UST	ADA	Placebo	Uncertainties / Strength of evidence	References
	Favourable Effects							
PASI 90	90% reduction on PASI score at wk 16 N (%) p value	%	M15-995 220/294 (74.8%) M16-008 229/304 (75.3%) M16-010 218/301 (72.4%)	M15-995 47/99 (47.5%) M16-008 42/100 (42%) <0.001	 M16-010 144/304 (47.4%) <0.001	M15-995 2/98 (2%) M16-008 5/102 (4.9%) <0.001	Less efficacy in heavier subjects	M15-995 M16-008 M16-010
sPGA 0/1	sPGA success (score 0/1) at wk 16 N (%)	%	M15-995 246/294 (83.7%) M16-008 267/304 (87.8%) M16-010 252/301 (83.7%)	M15-995 61/99 (61.6%) M16-008 63/100 (63%) < 0.001	 M16-010 183/304 (60.2%)	M15-995 5/98 (5.1%) M16-008 8/102 (7.8%)	Less efficacy in heavier subjects;	M15-995 M16-008 M16-010

Effect	Short Description	Unit	Risankizumab	UST	ADA	Placebo	Uncertainties / Strength of evidence	References
	p value				< 0.001	< 0.001		
PASI 100	100% reduction on PASI score at wk 52 N (%) p value	%	M15-995 175/294 (59.5%) M16-008 171/304 (56.3%)	M15-995 30/99 (30.3%) M16-008 21/100 (21%) < 0.001			Less efficacy in heavier subjects;	M15-995 M16-008
s PGA 0	s PGA score 0 at wk 52 N (%) p value	%	M15-995 175/294 (59.5%) M16-008 175/304 (57.6%) <0.001	M15-995 30/99 (30.3%) M16-008 21/100 (21%) < 0.001				M15-995 M16-008
DLQI (0,1)	Percentage of patients with a score of 0/1 at wk 16 N (%) p value	%	M15-995 196/294 (66.7%) M16-008 200/304 (65.8%)	M15-995 46/99 (46.5%) M16-008 43/100 (43%) <0.001	-	M15-995 4/98 (4.1%) M16-008 8/102 (7.8%) <0.001	Limited data provided	M15-995 M16-008

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Serious infections (MO)	1.7 1.8 1.6 (95% CI 1.1,2.3)	E/100 PY	RZB 150mg	(1)16 wk placebo: 1.1 (2) UST 52 weeks : 2.0 (3) no control: 77 wks	Although 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 and 4 reports of pneumonia,2 reports of osteomyelitis in the overall risankizumab treated population, over half of which were relate d to study drug and two of which resulted in discontinuation of study drug.	
Herpes Zoster	1) 0.2 2) 0.2 3) 0.4 (95% CI 0.13, 0.78)	E/100 PY		(1)16 wk placebo: 0.2 (2) UST 52 weeks : 1.5 (3) no control: 77 wks	There were 7 reports of herpes Zoster. 2 were reported as serious infections and 2 were considered related to study drug	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Fungal infection	5.2 4.2 3.4	E/100 PY	RZB 150mg	(1)16 wk vs. placebo: 0.3 (2) UST 52 weeks : 1.0 (3) no control: 77 wks	Tinea and Candidal fungal infections accounted for this increased reporting rate of fungal infections reported in the risankizumab groups across all analyses.	
Hepatic events	6.0 6.5 5.6 (95% CI 4.8,7.2)	E/100 PY		1)16 wk placebo: 7.6 (2) UST 52 weeks: 6.4 (3) Overall (no control)77 wks	3 possible cases of drug induced liver injury were reported following treatment with risankizumab -2 cases following treatment with 150mg risankizumab for psoriasis and 1 case following treatment with risankizumab 150mg for psoriatic arthritis.	
MACE	0.2 0.3 0.5 (95% CI 0.1,0.9)			1) placebo: 1.1 (2) UST 52 weeks: 0.0 (3) Overall (no control)77 wks	4 of 5 deaths were adjudicated as CV deaths. One was subsequently identified as a drug overdose.	
Extended MACE	0.5 0.6 0.7 (95% CI 4.1,1.32)			1) 16 wk placebo: 1.1 (2) UST 52 weeks : 0.0 (3) Overall (no control)77 wks		
Other CV events	0.5 1.3 0.8 (95% CI 0.4,1.3)			1) 16 wk placebo: 3.3 (2) UST 52 weeks : 0.0 (3) Overall (no control)77 wks		
Malignancy	1.5 0.5 1.5 (95% CI 0.96,2.19)			1) 16 wk placebo: 1.1 (2) UST 52 weeks : 0.5 (3) Overall (no control)77 wks		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that is directed against IL-23 p19 as a targeted biological treatment for patients with plaque psoriasis. Binding of risankizumab to IL-23 p19 inhibits the action of IL-23 to induce and sustain T helper (Th) 17 type cells, innate lymphoid cells, γδT cells, and natural killer (NK) cells responsible for tissue inflammation, destruction and aberrant tissue repair.

Risankizumab has been robustly demonstrated to work very effectively in a very heterogeneous population with moderate to severe plaque psoriasis and a significant proportion of patients achieved disease clearance. As the effect size of complete clearance – the desired treatment outcome - as measured by PASI 100 and sPGA-0 responders was also large.

Statistically significant results were demonstrated versus placebo and when compared with active treatment- Ustekinumab, this translated into an improvement in the quality of life and also demonstrated significant improvements in signs and symptoms of psoriasis.

Furthermore, improvements were demonstrated in patients not achieving an adequate response to Adalimumab therapy (PASI < 50, AND PASI 50-90) which may be a more treatment resistant population. Therefore, Risankizumab provides additional treatment options for a wide range of patients from naïve to systemic therapy through to those patients who are not adequately controlled on Adalimumab or ustekinumab. Improvements in regional psoriasis such as nail, scalp, foot and hand involvement were also demonstrated

Maintenance of effect was demonstrated. The vast majority of patients with continuous Risankizumab treatment at 52 weeks maintained their initial PASI and s PGA responses seen at week 16.

Subgroups analyses showed a consistently superior effect compared to placebo and active comparator Ustekinumab and no notable differences in efficacy were seen.

The most relevant safety concerns identified so far with treatment with risankizumab are related to infections, (serious infection, fungal infections, Herpes Zoster infections). The applicant has committed to including serious infections as a safety outcome in the planned post-marketing registry-based cohort study, (category 3 in the RMP) and further evaluating the risks of serious infections in psoriasis patients exposed to risankizumab relative to similar patients on other systemic psoriasis treatments. Although the overall rate of serious infections is comparable to other similar type agents the progression of serious infections to cases of sepsis is a concern. Serious infection is identified as a potential risk in the RMP and the applicant plans to conduct a post-marketing safety study to further monitor serious infections that require hospitalisation.

Three cases of drug induced hepatotoxicity were identified in the overall risankizumab development plan. These were heavily confounded were unlikely to be attributed to treatment with risankizumab. Two additional hepatic SAEs were identified in the SUR. (autoimmune hepatitis; hepatic cirrhosis). Regarding malignancies there was a slightly higher rate of malignancy seen with risankizumab compared with similar agents. Further longer term data is needed to fully characterise the risk of malignancies. This will be monitored in the ongoing long term study mentioned in the RMP.

The effect of risankizumab on cardiovascular system over longer term exposure should continue to be monitored. MACE is included as a potential risk in the RMP. Additional safety-related issues concerning safety in patients >65yrs, clinical impact of immunogenicity has been addressed by the section 4.8 of the SmPC.

3.7.2. Balance of benefits and risks

The efficacy of Risankizumab in the treatment of moderate to severe plaque psoriasis was robustly demonstrated across a wide population as need in treatment naïve, previous systemic therapy and in disease severity. The onset was achieved near maximal effect at week 16 and maintenance of effect was demonstrated to 52 weeks. The effect size was highly statistically significant, clinically relevant and superior to two active comparators.

Overall risankizumab has a low rate of adverse events which is comparable to placebo and generally more favourable than ustekinumab and adalimumab. Other concerns identified include fungal infections, MACE over longer term exposure. Safety data in patients >65 is limited as stated in the SmPC. Longer term data (>18months) is limited however an OLE study (M15-997) over 3years is ongoing (listed as category 3 in the RMP) and will provide further long term data. Overall, based on the data presented, the beneficial effects outweigh the unfavourable effects seen in the clinical programme.

Risankizumab can be self-administered which after initial treatment (loading dose and 4 weeks) is administered every 12 weeks this is considered convenient for patients as it limits the number of subcutaneous injections. Furthermore, as the frequency is every 12 weeks' compliance should not pose a concern this was also reflected in the trials.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Skyrizi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Skyrizi is favourable in the following indication:

Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of

an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that risankizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.