NAME OF THE MEDICINAL PRODUCT

Skyrizi 150 mg solution for injection in pre-filled pen
Skyrizi 150 mg solution for injection in pre-filled syringe
Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only)
Skyrizi Solution for Injection in Pre-filled Cartridge with On-body Injector 360mg/2.4mL

QUALITATIVE AND QUANTITATIVE COMPOSITION

Skyrizi 150 mg solution for injection in pre-filled pen

Each pre-filled pen contains 150 mg risankizumab in 1 mL solution.

Skyrizi 150 mg/mL contains less than 1 mmol sodium (23 mg) per 150 mg dose, i.e., essentially 'sodium-free'.

Solution for injection (injection).
The solution is colourless to yellow and clear to slightly opalescent.

Skyrizi 150 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 150 mg risankizumab in 1 mL solution.

Skyrizi 150 mg/mL contains less than 1 mmol sodium (23 mg) per 150 mg dose, i.e., essentially 'sodium-free'.

Solution for injection (injection).
The solution is colourless to yellow and clear to slightly opalescent.

Skyrizi Solution for Injection in Pre-filled Cartridge 360mg/2.4mL

Each 360 mg/2.4 mL prefilled cartridge contains 360 mg risankizumab in 2.4 mL solution.

Skyrizi 360 mg/2.4 mL contains less than 1 mmol sodium (23 mg) per 360 mg dose, i.e., essentially 'sodium-free'.

Solution for injection (injection).
The solution is colourless to yellow and clear to slightly opalescent.

Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only).

Each 600 mg/10.0 mL single-dose vial contains 600 mg in 10.0 mL solution.

Skyrizi 600 mg/10.0 mL contains less than 1 mmol sodium (23 mg) per 600 mg dose, i.e., essentially 'sodium-free'.

Solution for infusion.
The solution is colourless to slightly yellow and clear to slightly opalescent.

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody selective to the interleukin (IL)-23 protein produced in Chinese Hamster Ovary cells using recombinant DNA technology.

CLINICAL PARTICULARS

Therapeutic indications

Skyrizi 150 mg solution for injection in pre-filled pen and pre-filled syringe

Plaque Psoriasis
Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriatic Arthritis
Skyrizi, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

Palmoplantar Pustulosis
Skyrizi is indicated for the treatment of moderate to severe palmoplantar pustulosis in adults who do not adequately respond or are intolerant to conventional therapy.

Skyrizi Solution for Injection in Pre-filled Cartridge with On-body Injector 360mg/2.4mL/ Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only)

Crohn's Disease
Skyrizi is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

Posology and method of administration

Skyrizi is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Skyrizi is indicated.

Posology

Plaque Psoriasis, Psoriatic Arthritis and Palmoplantar Pustulosis

Skyrizi 150 mg solution for injection in pre-filled pen and pre-filled syringe

The recommended dose is 150 mg administered as a subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.

Some plaque psoriasis patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment.

Patients with palmoplantar pustulosis generally achieve a clinical response to treatment with risankizumab within 28 weeks of treatment initiation. If no response to treatment is achieved within 28 weeks, carefully reconsider whether to continue the treatment protocol with risankizumab.

Crohn's Disease

Skyrizi Solution for Injection in Pre-filled Cartridge with On-body Injector 360mg/2.4mL/ Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only)

The recommended dose is 600 mg administered by intravenous (IV) infusion at week 0, week 4, and week 8, followed by 360 mg administered by subcutaneous (SC) injection at week 12, and every 8

weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly (aged 65 years and over)

No dose adjustment is required (see **Pharmacokinetic properties** section).
There is limited information in subjects aged ≥65 years.

Renal or hepatic impairment

No specific studies were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of risankizumab. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary (see **Pharmacokinetic properties** section).

Paediatric population

The safety and efficacy of risankizumab in children and adolescents with plaque psoriasis or psoriatic arthritis aged 5 to 18 years have not yet been established. No data are available.

There is no relevant use of risankizumab in children aged below 6 years for the indication of moderate to severe plaque psoriasis or in children aged below 5 years for the indication of psoriatic arthritis.

The safety and efficacy of risankizumab in patients with Crohn's disease younger than 18 years of age have not yet been established.

Overweight patients

No dose adjustment is required (see **Pharmacokinetic properties** section).

Method of administration

Preparation and Administration Instructions (Plaque Psoriasis, Psoriatic Arthritis and Palmoplantar Pustulosis)

Skyrizi 150 mg solution for injection in pre-filled pen and pre-filled syringe

- Administer Skyrizi prefilled pen or prefilled syringe(s) subcutaneously.
- Patients may self-inject Skyrizi after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of Skyrizi.
- Before injecting, remove the carton with Skyrizi from the refrigerator and without removing the prefilled pen or prefilled syringe(s) from the carton, allow Skyrizi to reach room temperature out of direct sunlight (30 to 90 minutes for the prefilled pen and 15 to 30 minutes for the prefilled syringe(s)).
- When using Skyrizi 150 mg/mL prefilled pen or prefilled syringe, inject one 150 mg single-dose prefilled pen or prefilled syringe.

- Do not inject into areas where the skin is tender, bruised, erythematous, indurated or affected by psoriasis. Administration of Skyrizi in the upper, outer arm may only be performed by a healthcare professional or caregiver.
- If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.
- The Skyrizi "Instructions for Use" contains more detailed instructions on the preparation and administration of Skyrizi *[see Instructions for Use]*. Instruct the patient to read the Instructions for Use before administration.

Preparation and Administration Instructions (Crohn's Disease)

Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only).

Intravenous Induction Dosing Regimen:

1. Skyrizi should be prepared by a healthcare professional using aseptic technique.

2. Prior to administration, Skyrizi for intravenous administration must be diluted into an intravenous infusion bag or glass bottle containing 5% dextrose in water (D5W) or 0.9% saline (600 mg/10 mL in 100 mL, or 250 mL or 500 mL) to a final drug concentration of approximately 1.2 mg/mL to 6 mg/mL.

3. The solution in the vial and dilutions should not be shaken.

4. Prior to the start of the intravenous infusion, the content of the infusion bag or glass bottle should be at room temperature.

5. Infuse the diluted solution over a period of at least one hour. The infusion should be completely administered within 8 hours of the dilution in the infusion bag.

6. Skyrizi vial solution should not be administered concomitantly in the same intravenous line with other medicinal products.

7. Each vial is for single use only and any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Skyrizi Solution for Injection in Pre-filled Cartridge with On-body Injector 360mg/2.4mL

Subcutaneous Maintenance Dosing Regimen:

- Administer Skyrizi prefilled cartridge with on-body injector subcutaneously.
- Do not inject into areas where the skin is tender, bruised, erythematous, indurated or affected by any lesions.
- Patients may self-inject Skyrizi using the prefilled cartridge with on-body injector after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of Skyrizi.
- Before using the prefilled cartridge with on-body injector remove the carton from the refrigerator and allow to reach room temperature out of direct sunlight (45 to 90 minutes) without removing the on-body injector or prefilled cartridge from the carton.
- If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

- The Skyrizi "Instructions for Use" contains more detailed instructions on the preparation and administration of Skyrizi. Instruct the patient to read the Instructions for Use before administration.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in **List of excipients** section.

Clinically important active infections (e.g. active tuberculosis, see **warnings and precautions** section).

Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Risankizumab may increase the risk of infection.

In patients with a chronic infection, a history of recurrent infection, or known risk factors for infection, risankizumab should be used with caution. Treatment with risankizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Patients treated with risankizumab should be instructed to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops such an infection or 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.

Tuberculosis

Prior to initiating treatment with risankizumab, patients should be evaluated for tuberculosis (TB) infection. Patients receiving risankizumab should be monitored for signs and symptoms of active TB. Anti-TB therapy should be considered prior to initiating risankizumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Immunisations

Prior to initiating therapy with risankizumab, completion of all appropriate immunisations should be considered according to current immunisation guidelines. If a patient has received live vaccination (viral or bacterial), it is recommended to wait at least 4 weeks prior to starting treatment with risankizumab. Patients treated with risankizumab should not receive live vaccines during treatment and for at least 21 weeks after treatment (see **Pharmacokinetic properties** section).

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of risankizumab. If a serious hypersensitivity reaction occurs, administration of risankizumab should be discontinued immediately and appropriate therapy initiated.

Excipients with known effect

Skyrizi 150 mg solution for injection in pre-filled pen and pre-filled syringe

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled pen or pre-filled syringe, that is to say essentially ‘sodium free’.

Skyrizi Solution for Injection in Pre-filled Cartridge 360mg/2.4mL

This medicinal product contains less than 1 mmol sodium (23 mg) per cartridge, that is to say essentially ‘sodium-free’.

Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only).

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium free’.

Interaction with other medicinal products and other forms of interaction

Risankizumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. Drug interactions between risankizumab and inhibitors, inducers, or substrates of medicinal product metabolising enzymes are not expected and no dose adjustment is needed (see **Pharmacokinetic properties** section).

Concomitant immunosuppressive therapy or phototherapy

The safety and efficacy of risankizumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.

Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 21 weeks after treatment.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of risankizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of risankizumab during pregnancy.

Breast-feeding

It is unknown whether risankizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. A decision should be made whether to discontinue/abstain from risankizumab therapy, taking into account the benefit of breast-feeding to the child and the benefit of risankizumab therapy to the woman.

Fertility

The effect of risankizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Effects on ability to drive and use machines

Risankizumab has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were upper respiratory infections (from 13% in psoriasis to 15.6% in Crohn's disease).

Tabulated list of adverse reactions

Adverse reactions for risankizumab from clinical studies (Table 1) are listed by MedDRA system organ class and are based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000).

Table 1: List of adverse reactions

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Very common	Upper respiratory infections[a]
	Common	Tinea infections[b]
	Uncommon	Folliculitis
Immune system disorders	Rare	Anaphylactic reactions
Nervous system disorders	Common	Headache[c]
Skin and subcutaneous tissue disorders	Common	Pruritus Rash Eczema
	Uncommon	Urticaria
General disorders and administration site conditions	Common	Fatigue[d] Injection site reactions[e]

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis, laryngitis, tracheitis
[b] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, onychomycosis, fungal skin infection, tinea infection
[c] Includes: headache, tension headache, sinus headache
[d] Includes: fatigue, asthenia
[e] Includes: injection site bruising, erythema, haematoma, haemorrhage, irritation, pain, pruritus, reaction, swelling, induration, rash, hypersensitivity, nodule, urticaria, vesicles and warmth

Description of selected adverse reactions

Infections

Plaque Psoriasis

The rate of infections was 75.5 events per 100 subject-years from the psoriasis clinical studies and 43.0 events per 100 subject-years from the psoriatic arthritis clinical studies, including long-term exposure to risankizumab. The majority of cases were non-serious and mild to moderate in severity and did not lead to discontinuation of risankizumab. The rate of serious infections was 1.7 events per 100 subject-years from the psoriasis studies and 2.6 events per 100 subject-years from the psoriatic arthritis studies (see **warnings and precautions** section).

Long-term Safety

Through week 52, the frequency of the adverse reactions was similar to the safety profile observed during the first 16 weeks of treatment. Through week 52, the exposure-adjusted rates of serious adverse events per 100 subject-years were 9.4 for subjects treated with risankizumab and 10.9 for those treated with ustekinumab.
Patients who completed some of the Phase 3 plaque psoriasis clinical studies had the opportunity to enroll in the open-label extension study, LIMMITLESS. A total of 2170 subjects in the LIMMITLESS study were treated with risankizumab, representing 11586 subject-years of exposure. From first exposure to risankizumab, 2139 subjects with psoriasis were exposed to risankizumab for at least one year, and 1419 subjects were exposed for more than 5 years.

For those subjects exposed to more than 5 years of risankizumab, no new adverse reactions were identified compared with the first 16 weeks of treatment.

Psoriatic arthritis

Overall, the safety profile observed in patients with psoriatic arthritis treated with risankizumab was consistent with the safety profile observed in patients with plaque psoriasis.

Palmoplantar Pustulosis

Overall, the safety profile observed in patients with palmoplantar pustulosis treated with risankizumab was consistent with the safety profile observed in patients with plaque psoriasis. The safety profile of risankizumab with up to 76 weeks of exposure was consistent with the profile observed with the first 16 weeks.

Crohn's Disease

Overall, the safety profile observed in patients with Crohn's disease treated with risankizumab was consistent with the safety profile observed in patients with plaque psoriasis.

The rate of infections in the pooled data from the 12-week induction studies was 83.3 events per 100 subject-years in subjects treated with risankizumab 600 mg intravenously compared to 117.7 events per 100 subject-years in placebo. The rate of serious infections was 3.4 events per 100 subject-years in subjects treated with risankizumab 600 mg intravenously compared to 16.7 events per 100 subject-years in placebo (see warnings and precautions section).

The rate of infections in the 52-week maintenance study was 57.7 events per 100 subject-years in subjects treated with risankizumab 360 mg subcutaneously after risankizumab induction compared to 76.0 events per 100 subject-years in subjects who received placebo after risankizumab induction. The rate of serious infections was 6.0 events per 100 subject-years in subjects treated with risankizumab 360 mg subcutaneously after risankizumab induction compared to 5.0 events per 100 subject-years in subjects who received placebo after risankizumab induction (see warnings and precautions section).

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with risankizumab. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

Plaque Psoriasis

For subjects treated with risankizumab at the recommended clinical dose for up to 52 weeks in psoriasis clinical trials, treatment-emergent anti-drug antibodies and neutralising antibodies were detected in 24% (263/1,079) and 14% (150/1,079) of evaluated subjects, respectively. For subjects

exposed to long term treatment of risankizumab in the extension study, the immunogenicity profile observed up to 204 weeks of treatment was consistent compared to the first 52 weeks of treatment.

For most subjects with psoriasis, antibodies to risankizumab including neutralising antibodies were not associated with changes in clinical response or safety. Among the few subjects (approximately 1%; 7/1,000 at week 16 and 6/598 at week 52) with high antibody titres (>128), clinical response appeared to be reduced. The incidence of injection site reactions is numerically higher in the anti-drug antibody-positive compared with anti-drug antibody-negative groups over short-term (16 weeks: 2.7% vs 1.3%) and longer term treatment (>52 weeks: 5.0% vs 3.3%). The injection site reactions were all mild to moderate in severity, none were serious, and none led to discontinuation of risankizumab.

For subjects treated with risankizumab at the recommended clinical dose for up to 28 weeks in psoriatic arthritis clinical trials, treatment-emergent anti-drug antibodies and neutralizing antibodies were detected in 12.1% (79/652) and 0% (0/652) of evaluated subjects, respectively. Antibodies to risankizumab were not associated with changes in clinical response or safety for psoriatic arthritis.

Palmoplantar Pustulosis

For subjects treated with risankizumab at the recommended clinical dose for up to 68 weeks in the palmoplantar pustulosis clinical trial, treatment emergent anti-drug antibodies and neutralizing antibodies were detected in 11.7% (7/60) and 10% (6/60) of evaluated subjects, respectively.

Crohn's Disease

For subjects with Crohn's disease treated with risankizumab at the recommended intravenous induction and subcutaneous maintenance doses for up to 64 weeks in CD clinical trials, treatment-emergent anti-drug antibodies and neutralizing antibodies were detected in 3.4% (2/58) and 0% (0/58) of evaluated subjects, respectively.

Across all indications, antibodies to risankizumab including neutralizing antibodies were not associated with changes in clinical response or safety.

Elderly

There is limited safety information in subjects aged ≥65 years.

Post Marketing Experience
The following adverse reactions have been identified during post-approval use of risankizumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Skin and subcutaneous tissue disorders: eczema, rash, and urticaria
Immune system disorders: anaphylactic reaction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

Overdose

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC18

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 without binding to IL-12 and inhibits its interaction with the IL-23 receptor complex. IL-23 is a cytokine that is involved in inflammatory and immune responses. IL-23 is elevated in inflamed colonic mucosa from Crohn's patients compared to colonic mucosa from healthy individuals. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Pharmacodynamic effects

In a study of subjects with psoriasis, expression of genes associated with the IL-23/IL-17 axis was decreased in the skin after single doses of risankizumab. Reductions in epidermal thickness, infiltration of inflammatory cells, and expression of psoriatic disease markers were also observed in psoriatic lesions.

In a study of subjects with psoriatic arthritis, statistically significant and clinically meaningful reduction from baseline was observed at week 24 in IL-23 and IL-17-associated biomarkers, including serum IL-17A, IL-17F, and IL-22 following treatment with risankizumab 150 mg subcutaneously at week 0, week 4, and every 12 weeks thereafter.

In a Phase 2 study of subjects with Crohn's disease, expression of genes associated with the IL-23/Th17 axis was decreased in gut tissue after multiple doses of risankizumab. Reductions in fecal calprotectin (FCP), serum C reactive protein (CRP) and IL-22 were also observed after multiple doses in Phase 3 induction studies in Crohn's patients. Decreases in FCP, CRP and serum IL-22 were maintained out to week 52 of the maintenance study.

Clinical efficacy and safety

Plaque Psoriasis

The efficacy and safety of risankizumab was assessed in 2,109 subjects with moderate to severe plaque psoriasis in four multicentre, randomised, double-blind studies (ULTIMMA-1, ULTIMMA-2, IMMHANCE, and IMMVENT). Patients who completed these studies had the opportunity to enroll in the open-label extension study, LIMMITLESS. Enrolled subjects were 18 years of age and older with plaque psoriasis who had a body surface area (BSA) involvement of ≥10%, a static Physician Global Assessment (sPGA) score of ≥3 in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 4, a Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for systemic therapy or phototherapy.

Overall, subjects had a median baseline PASI score of 17.8, a median BSA of 20.0%, and a median baseline DLQI score of 13.0. Baseline sPGA score was severe in 19.3% of subjects and moderate in 80.7% of subjects. A total of 9.8% of study subjects had a history of diagnosed psoriatic arthritis.

Across all studies, 30.9% of subjects were naïve to any systemic therapy (including non-biologic and biologic), 38.1% had received prior phototherapy or photochemotherapy, 48.3% had received prior non-biologic systemic therapy, 42.1% had received prior biologic therapy, and 23.7% had received at least one anti-TNF alpha agent for the treatment of psoriasis.

ULTIMMA-1 and ULTIMMA-2

ULTIMMA-1 and ULTIMMA-2 enrolled 997 subjects (598 randomised to risankizumab 150 mg, 199 to ustekinumab 45 mg or 90 mg [according to baseline weight], and 200 to placebo). Subjects received treatment at week 0, week 4, and every 12 weeks thereafter. The two co-primary endpoints in ULTIMMA-1 and ULTIMMA-2 were the proportion of subjects who achieved 1) PASI 90 response and 2) sPGA score of clear or almost clear (sPGA 0 or 1) at week 16 versus placebo. The results for the co-primary and other endpoints are presented in Table 2 and Figure 1.

Table 2: Efficacy and quality of life results in adults with plaque psoriasis in ULTIMMA-1 and ULTIMMA-2

	ULTIMMA-1			**ULTIMMA-2**		
	Risankizumab (N=304) n (%)	**Ustekinumab (N=100) n (%)**	**Placebo (N=102) n (%)**	**Risankizumab (N=294) n (%)**	**Ustekinumab (N=99) n (%)**	**Placebo (N=98) n (%)**
sPGA of clear or almost clear (0 or 1)						
Week 16[a]	267 (87.8)	63 (63.0)	8 (7.8)	246 (83.7)	61 (61.6)	5 (5.1)
Week 52	262 (86.2)	54 (54.0)	--	245 (83.3)	54 (54.5)	--
sPGA of clear (0)						
Week 16	112 (36.8)	14 (14.0)	2 (2.0)	150 (51.0)	25 (25.3)	3 (3.1)
Week 52	175 (57.6)	21 (21.0)	--	175 (59.5)	30 (30.3)	--
PASI 75						
Week 12	264 (86.8)	70 (70.0)	10 (9.8)	261 (88.8)	69 (69.7)	8 (8.2)
Week 52	279 (91.8)	70 (70.0)	--	269 (91.5)	76 (76.8)	--
PASI 90						
Week 16[a]	229 (75.3)	42 (42.0)	5 (4.9)	220 (74.8)	47 (47.5)	2 (2.0)
Week 52	249 (81.9)	44 (44.0)	--	237 (80.6)	50 (50.5)	--
PASI 100						
Week 16	109 (35.9)	12 (12.0)	0 (0.0)	149 (50.7)	24 (24.2)	2 (2.0)
Week 52	171 (56.3)	21 (21.0)	--	175 (59.5)	30 (30.3)	--
DLQI 0 or 1[b]						
Week 16	200 (65.8)	43 (43.0)	8 (7.8)	196 (66.7)	46 (46.5)	4 (4.1)
Week 52	229 (75.3)	47 (47.0)	--	208 (70.7)	44 (44.4)	--
PSS 0 (symptom-free)[c]						
Week 16	89 (29.3)	15 (15.0)	2 (2.0)	92 (31.3)	15 (15.2)	0 (0.0)
Week 52	173 (56.9)	30 (30.0)	--	160 (54.4)	30 (30.3)	--

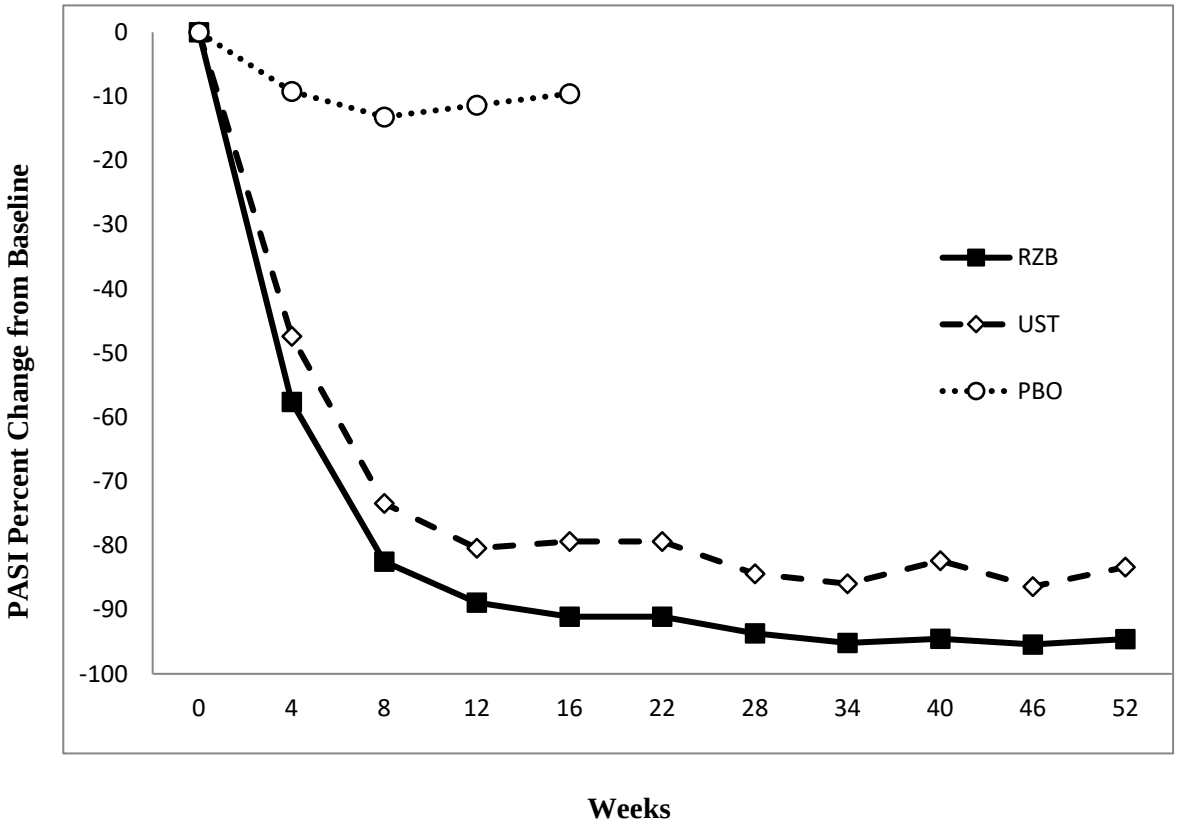
All comparisons of risankizumab versus ustekinumab and placebo achieved $p<0.001$ except for PASI 75 at week 52 in ULTIMMA-2 where $p=0.001$

[a] Co-primary endpoints versus placebo

[b] No impact on health-related quality of life

[c] Psoriasis Symptom Scale (PSS) of 0 means no symptoms of pain, itching, redness, and burning during the last 24 hours

Figure 1: Time course of mean percent change from baseline of PASI in ULTIMMA-1 and ULTIMMA-2



RZB = risankizumab
UST = ustekinumab
PBO = placebo
p<0.001 at each time point

Examination of age, gender, race, body weight ≤130 kg, baseline PASI score, concurrent psoriatic arthritis, previous non-biologic systemic treatment, previous biologic treatment, and previous failure of a biologic did not identify differences in response to risankizumab among these subgroups.

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.

Table 3: 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: Change at week 16 (SE)	N=95; -5.93 (0.324)	N=34; -3.17 (0.445) ***	N=86; -7.24 (0.558)	N=23; -3.74 (1.025) **	N=113; -7.39 (0.654)	N=26; -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	N=178; -15.7 (0.94)	-	N=183; -16.7 (0.85)	-	-	-

52 (SE)						
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						

Anxiety and depression, as measured by the Hospital Anxiety and Depression Scale (HADS), improved in the risankizumab group at week 16 compared with the placebo group.

Maintenance of response

In an integrated analysis of subjects receiving risankizumab in ULTIMMA-1 and ULTIMMA-2 for PASI 100 responders at week 16, 79.8% (206/258) of the subjects who continued on risankizumab maintained the response at week 52. For PASI 90 responders at week 16, 88.4% (398/450) of subjects maintained the response at week 52.

Of the patients who received risankizumab in ULTIMMA-1 and ULTIMMA-2, 525 continued to receive risankizumab every 12 weeks in LIMMITLESS. Of these, 376 (71.6%) completed an additional 252 weeks of open-label treatment. Among subjects remaining in the study, improvements achieved with risankizumab in rates of PASI 90 and sPGA of clear or almost clear at week 52 were maintained through week 304.

Of the patients who received ustekinumab in ULTIMMA-1 and ULTIMMA-2, 172 received risankizumab every 12 weeks in LIMMITLESS. Of these, 116 (67.4%) completed the study, including 252 weeks of open-label risankizumab treatment and end of study follow-up. Among subjects remaining in the study, rates of PASI 90 and sPGA response of clear or almost clear increased from week 52 through week 76 and were then maintained through week 304.

Figures 2 and 3 show the response rates for PASI 90 and sPGA of clear or almost clear, respectively, in subjects who completed 252 weeks of open-label treatment in LIMMITLESS.

Figure 2: Percent of subjects who achieved a PASI 90 response (OC) in LIMMITLESS

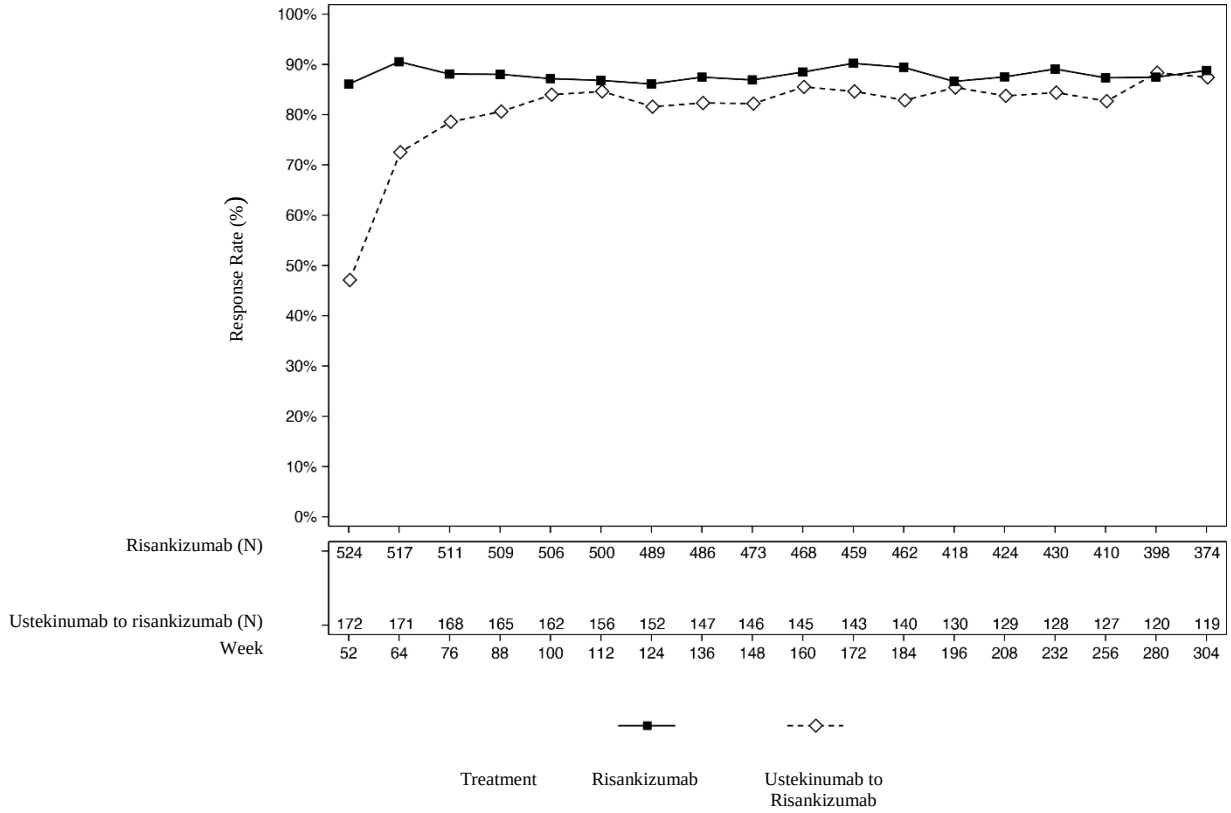
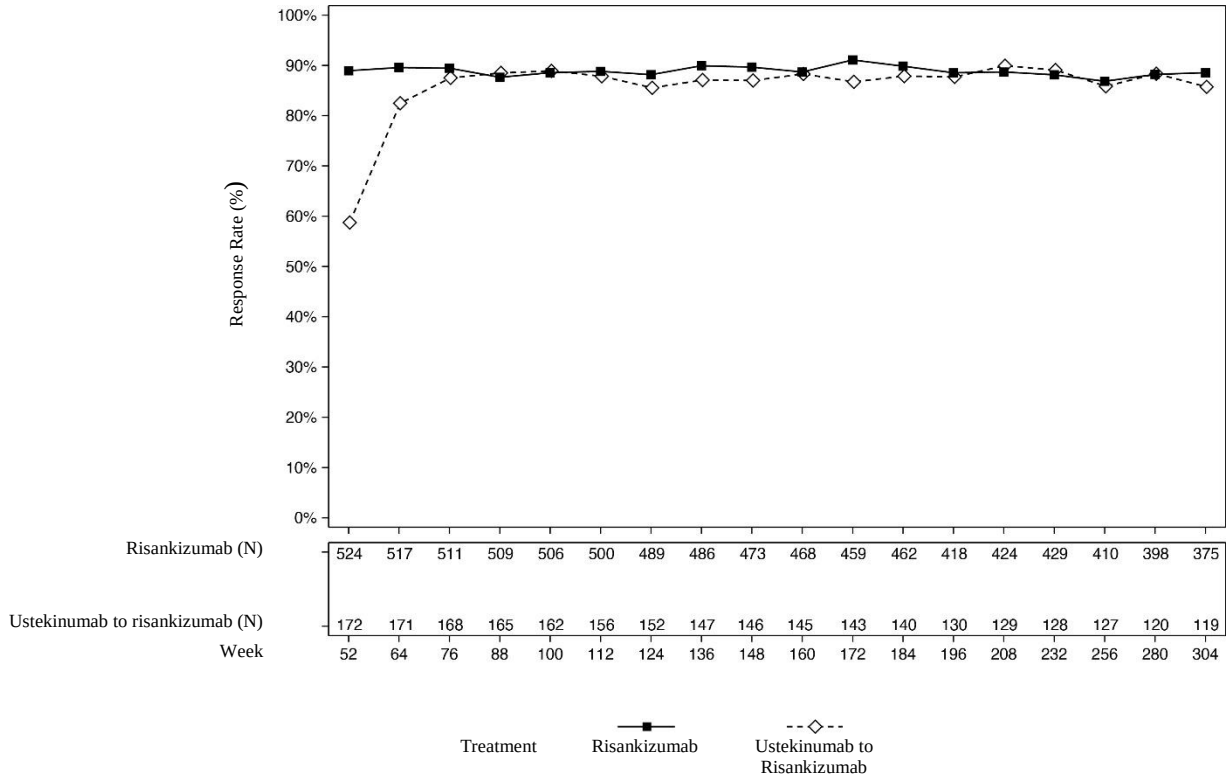


Figure 3: Percent of subjects who achieved an sPGA clear or almost clear response by visit (OC) in LIMMITLESS



Improvements in Dermatology Life Quality Index (DLQI 0 or 1) were maintained in patients receiving continuous risankizumab treatment through week 304 in the open label extension study LIMMITLESS.

The safety profile of risankizumab with more than 5 years of exposure was consistent with the profile observed up to 16 weeks.

IMMHANCE

IMMHANCE enrolled 507 subjects (407 randomised to risankizumab 150 mg and 100 to placebo). Subjects received treatment at week 0, week 4 and every 12 weeks thereafter.

At week 16, risankizumab was superior to placebo on the co-primary endpoints of sPGA of clear or almost clear (83.5% risankizumab vs 7.0% placebo) and PASI 90 (73.2% risankizumab vs 2.0% placebo).

Of the 31 subjects from the IMMHANCE study with latent tuberculosis (TB) who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on risankizumab.

Among subjects with sPGA of clear or almost clear at week 28 in IMMHANCE, 81.1% (90/111) of subjects re-randomised to continued treatment with risankizumab maintained this response at week 104 compared with 7.1% (16/225) who were re-randomised to withdrawal from risankizumab. Of these subjects, 63.1% (70/111) of subjects re-randomised to continued treatment with risankizumab achieved a sPGA clear response at week 104 compared with 2.2% (5/225) who were re-randomised to withdrawal from risankizumab.

Among subjects who achieved sPGA of clear or almost clear at week 28 and relapsed to sPGA of moderate or severe following withdrawal from risankizumab, 83.7% (128/153) regained sPGA of clear or almost clear after 16 weeks of retreatment. Loss of sPGA of clear or almost clear was observed as early as 12 weeks after a missed dose. Of those subjects who were re-randomised to withdraw from treatment, 80.9% (182/225) relapsed, and the median time to relapse was 295 days. No characteristics were identified to predict the time to loss of response or likelihood of regaining response at the individual patient level.

IMMVENT

IMMVENT enrolled 605 subjects (301 randomised to risankizumab and 304 to adalimumab). Subjects randomised to risankizumab received 150 mg of treatment at week 0, week 4 and every 12 weeks thereafter. Subjects randomised to adalimumab received 80 mg at week 0, 40 mg at week 1 and 40 mg every other week through week 15. Starting at week 16, subjects who were receiving adalimumab continued or switched treatment based on response:

- <PASI 50 were switched to risankizumab
- PASI 50 to <PASI 90 were re-randomised to either continue adalimumab or switch to risankizumab
- PASI 90 continued to receive adalimumab

Results are presented in Table 4.

Table 4: Efficacy and quality of life results at week 16 in adults with plaque psoriasis in IMMVENT

	Risankizumab (N=301) n (%)	Adalimumab (N=304) n (%)
sPGA of clear or almost clear[a]	252 (83.7)	183 (60.2)
PASI 75	273 (90.7)	218 (71.7)
PASI 90[a]	218 (72.4)	144 (47.4)
PASI 100	120 (39.9)	70 (23.0)
DLQI 0 or 1[b]	198 (65.8)	148 (48.7)
All comparisons achieved p<0.001 [a] Co-primary endpoints [b] No impact on health-related quality of life		

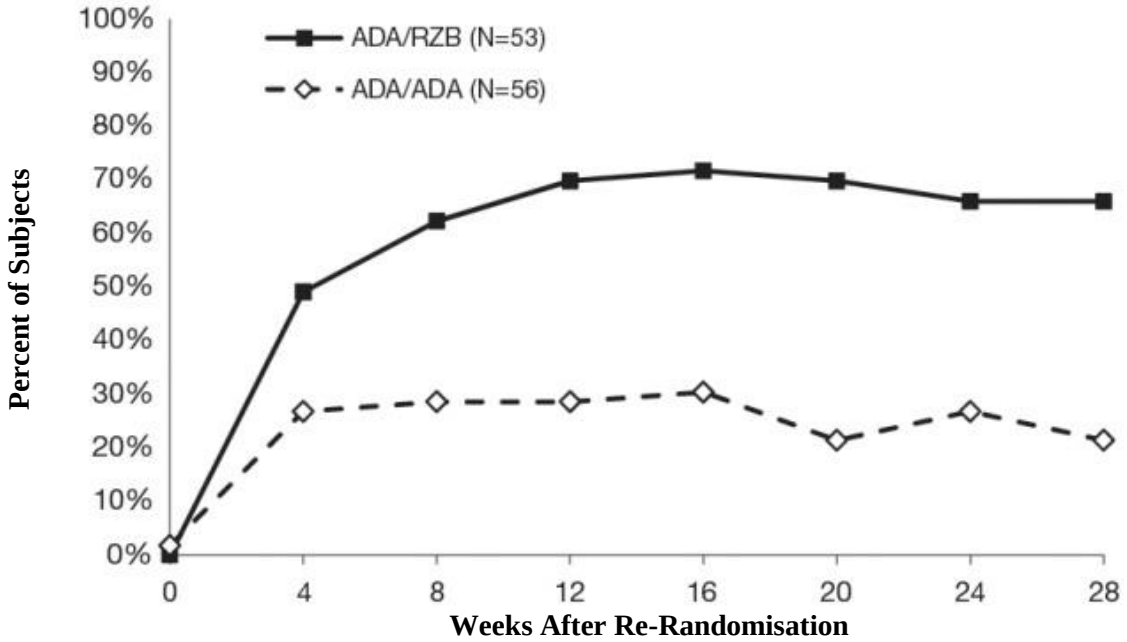
For subjects who had PASI 50 to <PASI 90 with adalimumab at week 16 and were re-randomised, differences in PASI 90 response rates between switching to risankizumab and continuing adalimumab were noted 4 weeks after re-randomisation (49.1% vs 26.8%, respectively).

Results 28 weeks after re-randomisation are presented in Table 5 and Figure 4.

Table 5: Efficacy results 28 weeks after re-randomisation in IMMVENT

	Switched to Risankizumab (N=53) n (%)	Continued on Adalimumab (N=56) n (%)
PASI 90	35 (66.0)	12 (21.4)
PASI 100	21 (39.6)	4 (7.1)
All comparisons achieved p<0.001		

Figure 4: Time course of PASI 90 after re-randomisation in IMMVENT



ADA/ADA: Subjects randomised to adalimumab and continued on adalimumab
ADA/RZB: Subjects randomised to adalimumab and switched to risankizumab
p<0.05 at week 4 and p<0.001 at each time point beginning at week 8

In 270 subjects who switched from adalimumab to risankizumab without a washout period, the safety profile of risankizumab was similar to that in subjects who initiated risankizumab after wash out of any prior systemic therapies.

Psoriatic Arthritis

Risankizumab has been shown to improve signs and symptoms, physical function, health-related quality of life, and the proportion of subjects with no radiographic progression in adults with active psoriatic arthritis (PsA).

The safety and efficacy of risankizumab were assessed in 1407 subjects with active PsA in 2 randomized, double-blind, placebo-controlled studies (964 in KEEPSAKE1 and 443 in KEEPSAKE2).

Subjects in these studies had a diagnosis of PsA for at least 6 months based on the Classification Criteria for Psoriatic Arthritis (CASPAR), a median duration of PsA of 4.9 years at baseline, ≥ 5 tender joints and ≥ 5 swollen joints, and active plaque psoriasis or nail psoriasis at baseline. 55.9% of subjects had ≥ 3% BSA with active plaque psoriasis. 63.4% and 27.9% of subjects had enthesitis and dactylitis, respectively. In KEEPSAKE1, where nail psoriasis was further assessed, 67.3% had nail psoriasis.

In both studies, subjects were randomized to receive risankizumab 150 mg or placebo at weeks 0, 4, and 16. Starting from week 28, all subjects received risankizumab every 12 weeks.

In KEEPSAKE1, all subjects had a previous inadequate response or intolerance to non-biologic DMARD therapy and were biologic naïve. In KEEPSAKE2, 53.5% of subjects had a previous inadequate response or intolerance to non-biologic DMARD therapy and 46.5% of subjects had a previous inadequate response or intolerance to biologic therapy.

In both studies, 59.6% of subjects were receiving concomitant methotrexate (MTX), 11.6% were receiving concomitant non-biologic DMARDs other than MTX, and 28.9% were receiving risankizumab monotherapy.

Clinical Response

Treatment with risankizumab resulted in significant improvement in measures of disease activity compared with placebo at week 24. For both studies, the primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response at week 24. The key efficacy results are shown in Table 6.

Table 6. Efficacy Results in Studies KEEPSAKE1 and KEEPSAKE2

	KEEPSAKE1		**KEEPSAKE2**	
Endpoint	**Placebo N=481 n (%)**	**risankizumab N=483 n (%)**	**Placebo N=219 n (%)**	**risankizumab N=224 n (%)**
ACR20 Response				
Week 16	161 (33.4)	272 (56.3)[a]	55 (25.3)	108 (48.3)[a]
Week 24	161 (33.5)	277 (57.3)[a]	58 (26.5)	115 (51.3)[a]
Week 52*	-	338/433 (78.1)	-	131/191 (68.6)
ACR50 Response				
Week 24	54 (11.3)	162 (33.4)[b]	20 (9.3)	59 (26.3)[b]
Week 52*	-	209/435 (48.0)	-	72/192 (37.5)
ACR70 Response				
Week 24	23 (4.7)	74 (15.3)[b]	13 (5.9)	27 (12.0)[c]

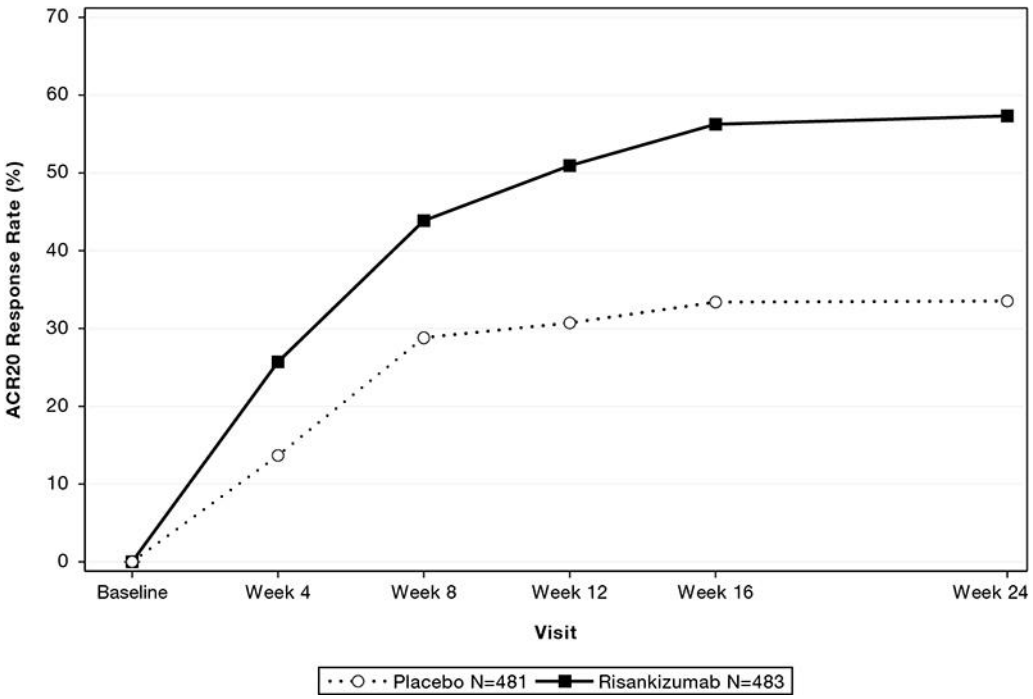
Week 52*	-	125/437 (28.6)	-	37/192 (19.3)
Resolution of Enthesitis (LEI=0)				
Week 24*	156/448 (34.8)[d]	215/444 (48.4)[a, d]	-	-
Week 52*	-	244/393 (62.1)[d]	-	-
Resolution of Dactylitis (LDI=0)				
Week 24*	104/204 (51.0)[e]	128/188 (68.1)[a, e]	-	-
Week 52*	-	143/171 (83.6)[e]	-	-
Minimal Disease Activity (MDA) Response				
Week 24	49 (10.2)	121 (25.0)[a]	25 (11.4)	57 (25.6)[a]
Week 52*	-	183/444 (41.2)	-	61/197 (31.0)

* Data are shown for available subjects in the format of n/N observed (%).
[a] Multiplicity-controlled p≤0.001 risankizumab vs placebo comparison.
[b] Nominal p≤0.001 risankizumab vs placebo comparison.
[c] Nominal p≤0.05 risankizumab vs placebo comparison.
[d] Summarized from pooled data from KEEPSAKE1 and KEEPSAKE2 for subjects with baseline LEI >0.
[e] Summarized from pooled data from KEEPSAKE1 and KEEPSAKE2 for subjects with baseline LDI >0.

Response over time

In KEEPSAKE1, a greater ACR20 response was observed in the risankizumab group compared to placebo as early as week 4 (25.7%) and the treatment difference continued over time to week 24 (Figure 5).

Figure 5. Percent of Subjects Achieving ACR20 Responses in Study KEEPSAKE1 through week 24



A greater ACR20 response for risankizumab versus placebo was seen as early as week 4 in 19.6% of subjects in KEEPSAKE2.

Responses observed in risankizumab groups were similar regardless of concomitant non-biologic DMARD use, number of prior non-biologic DMARDs, age, gender, race, and BMI. In KEEPSAKE2, responses were seen regardless of prior biologic therapy.

The safety profile of risankizumab with up to 52 weeks of exposure was consistent with the profile observed up to 24 weeks.

In both studies, the proportion of subjects achieving modified PsA Response Criteria (PsARC) at week 24 was higher in subjects receiving risankizumab compared with placebo. In addition, subjects receiving risankizumab achieved greater improvement in Disease Activity Score (28 joints) using CRP (DAS28-CRP) compared with placebo at week 24. Improvements were maintained through week 52 for PsARC and DAS28-CRP.

Treatment with risankizumab resulted in improvements in individual ACR components, Health Assessment Questionnaire-Disability Index (HAQ-DI), pain assessment, and high-sensitivity C-reactive protein (hsCRP) compared with placebo.

Treatment with risankizumab resulted in statistically significant improvement in the skin manifestations of psoriasis in subjects with psoriatic arthritis.

Treatment with risankizumab resulted in statistically significant improvement in the modified Nail Psoriasis Severity Index (mNAPSI) and the 5-point Physician's Global Assessment of Fingernail Psoriasis (PGA-F) scores in subjects with nail psoriasis at baseline (67.3%) in KEEPSAKE1. This improvement was maintained through week 52 (see Table 7).

Table 7. Nail Psoriasis Efficacy Results in KEEPSAKE1

	Placebo N=338	**risankizumab N=309**
mNAPSI change from baseline[a]		
Week 24	–5.57	–9.76[b]
Week 52	—	–13.64
PGA-F change from baseline[a]		
Week 24	–0.4	–0.8[b]
Week 52	—	–1.2
PGA-F clear/minimal and ≥2-grade improvement[c]		
Week 24 n (%)	30 (15.9)	71 (37.8)[d]
Week 52 n (%)	—	105 (58.0)

[a] Summarized for subjects with baseline nail psoriasis (Placebo N=338; risankizumab N=309; at week 52, for mNAPSI, observed risankizumab N=290, for PGA-F, observed risankizumab N=291).
[b] Multiplicity-controlled p≤0.001 risankizumab vs placebo comparison.
[c] Summarized for subjects with nail psoriasis and a PGA-F overall global assessment score of 'Mild', 'Moderate' or 'Severe' at Baseline (Placebo N=190; risankizumab N=188, at week 52 observed risankizumab N=181).
[d] Nominal p≤0.001 risankizumab vs placebo comparison.

Radiographic Response

In KEEPSAKE1, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified Total Sharp Score (mTSS) at week 24, compared with baseline. The mTSS score was modified for psoriatic arthritis by addition of hand distal interphalangeal (DIP) joints. At week 24, the mean progression of structural damage with risankizumab (mean mTSS 0.23) compared with placebo (mean mTSS 0.32) was not statistically significant. At week 24, the proportion

of subjects with no radiographic progression (defined as a change from baseline in mTSS ≤ 0) was higher with risankizumab (92.4%) compared with placebo (87.7%). This response was maintained through week 52.

Physical Function and Health Related Quality of Life

In both studies, subjects treated with risankizumab showed statistically significant improvement from baseline in physical function as assessed by HAQ-DI at week 24 (KEEPSAKE1 (-0.31) compared with placebo (-0.11) ($p \leq 0.001$)), (KEEPSAKE2 (-0.22) compared with placebo (-0.05) ($p \leq 0.001$)). At week 24, a greater proportion of subjects achieved a clinically meaningful reduction of at least 0.35 in HAQ-DI score from baseline in the risankizumab group compared with placebo. Improvements in physical function were maintained through week 52.

In both studies, subjects treated with risankizumab demonstrated significant improvements in the SF-36 V2 physical component summary scores and in FACIT-Fatigue scores at week 24, compared with placebo, with improvements maintained through week 52.

At baseline, psoriatic spondylitis was reported in 19.6% (7.9% diagnosed by radiograph or MRI) of subjects in KEEPSAKE1 and 19.6% (5% diagnosed by radiograph or MRI) of subjects in KEEPSAKE2. Subjects with clinically assessed psoriatic spondylitis who were treated with risankizumab showed improvements from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared with placebo at week 24. Improvements were maintained through week 52. There is insufficient evidence of the efficacy of risankizumab in subjects with radiograph- or MRI-confirmed ankylosing spondylitis-like psoriatic arthropathy due to the small number of subjects studied.

Palmoplantar Pustulosis

The efficacy and safety of risankizumab was assessed in 119 subjects with moderate to severe palmoplantar pustulosis in a randomized, double-blind, placebo-controlled study in Japanese subjects (jumPPP study). Enrolled subjects had PPPASI total score of ⩾ 12 and PPPASI severity score of pustules/vesicles on the palms or soles ⩾2.

Subjects were randomized to receive either risankizumab 150 mg SC or placebo SC at weeks 0 and 4. Subjects in the placebo treatment group received placebo at weeks 0, 4 and then received risankizumab 150 mg at weeks 16, 20, and every 12 weeks thereafter. Patients who received risankizumab 150 mg SC at week 0 and week 4 continued receiving risankizumab every 12 weeks thereafter.

Subject characteristics were similar among both treatment groups. All subjects received prior treatment for palmoplantar pustulosis including phototherapy, immunosuppressive agents and/or systemic corticosteroids.

Change from baseline in PPPASI total score (Changes in PPPASI score) at week 16 and 68 is shown in Table 8.

Table 8. Changes in PPPASI score [Mean (SE)]

	Placebo (N=58)	**risankizumab 150 mg (N=60)**	**P-value**
Week 16*	-8.48 (1.244)	-11.96 (1.223)	p<0.05

	Placebo/risankizumab 150 mg (N=55)	**risankizumab 150 mg/ risankizumab 150 mg (N=54)**	**P-value**
Week 68**	-21.77 (0.998)	-20.58 (1.008)	NA

*Week 16 results were based on MMRM model, with MMRM method to handle missing data.
**Week 68 results were based on ANCOVA model, with OC method to handle missing data.
Subjects treated with risankizumab achieved statistically significant improvements in PPPASI score at week 16 compared with placebo. These improvements were maintained through week 68. In subjects who started with placebo and switched to risankizumab at week 16, the trajectory of improvement was similar to that observed in subjects originally randomized to risankizumab over the same time interval after initiating risankizumab.

Subjects treated with risankizumab achieved statistically significant improvements in PPPASI score at week 16 compared with placebo. These improvements were maintained through week 68. In subjects who started with placebo and switched to risankizumab at week 16, the trajectory of improvement was similar to that observed in subjects originally randomized to risankizumab over the same time interval after initiating risankizumab.

Crohn's Disease

The efficacy and safety of risankizumab was assessed in 1419 subjects with moderately to severely active Crohn's disease in three multicenter, randomized, double-blind, placebo-controlled clinical studies. Enrolled subjects were 16 years of age or older with a Crohn's Disease Activity Index (CDAI) of 220 to 450, an average daily stool frequency (SF) ≥ 4 and/or average daily abdominal pain score (APS) ≥ 2, and a Simple Endoscopic Score for CD (SES-CD) of ≥ 6, or ≥4 for isolated ileal disease, excluding the narrowing component and confirmed by a central reviewer.

There were two 12-week intravenous induction studies (ADVANCE and MOTIVATE), which included a 12-week extension period for subjects who did not achieve SF/APS clinical response (≥ 30% decrease in SF and/or ≥ 30% decrease in APS and both not worse than baseline) at week 12. ADVANCE and MOTIVATE were followed by a 52-week randomized withdrawal study of subcutaneous maintenance treatment (FORTIFY) that enrolled subjects with SF/APS clinical response to IV induction treatment, representing at least 64 weeks of therapy.

ADVANCE and MOTIVATE

In studies ADVANCE and MOTIVATE, subjects were randomized to receive either risankizumab 600 mg IV (recommended dose), risankizumab 1,200 mg IV, or placebo, at week 0, week 4, and week 8.

In ADVANCE, 58% (491/850) subjects had failed or were intolerant to treatment with one or more biologic therapies (prior biologic failure), and 42% (359/850) had failed or were intolerant to treatment with conventional therapy but not to biologic therapy (without prior biologic failure). In ADVANCE, among the subjects without prior biologic failure, 87% (314/359) were naïve to biologic therapy and the remaining 13% had received biologic therapy but never failed nor demonstrated intolerance. All subjects in MOTIVATE had prior biologic failure.

In both studies, a greater proportion of subjects treated with risankizumab achieved the co-primary endpoints of clinical remission at week 12 and endoscopic response at week 12 compared to placebo. Enhanced SF/APS clinical response and clinical remission were significant as early as week 4 in subjects treated with risankizumab and continued to improve through week 12 (Table 9).

Table 9. Efficacy Results in ADVANCE and MOTIVATE

	ADVANCE			**MOTIVATE**		
	Placebo IV (N=175) %	**risankizumab 600 mg IV (N=336) %**	**Treatment differenced [d] (95% CI)**	**Placebo IV (N=187) %**	**risankizumab 600 mg IV (N=191) %**	**Treatment differenced (95% CI)[d]**

Co-primary endpoints						
Clinical Remission at week 12[e]	22%	43%	22% [14%, 30%][a]	19%	35%	15% [6%, 24%][b]
Endoscopic Response at week 12[f]	12%	40%	28% [21%, 35%][a]	11%	29%	18% [10%, 25%][a]
Additional endpoints						
Enhanced SF/APS Clinical Response at week 4[g]	31%	46%	15% [6%, 23%][b]	32%	45%[c]	14% [4%, 23%][c]
Enhanced SF/APS Clinical Response at week 12[g]	42%	63%	21% [12%, 30%][a]	39%	62%	23% [13%, 33%][a]
CDAI <150 at week 4	10%	18%	8% [1%, 14%][c]	11%	21%	10% [2%, 17%][c]
CDAI <150 at week 12	25%	45%	21% [12%, 29%][a]	20%	42%	22% [13%, 31%][a]
Mucosal healing at week 12[h]	(N=173) 8%	(N=336) 21%	14% [8%, 19%][a]	(N=186) 4%	(N=190) 14%	9% [4%, 15%][b]
Endoscopic Remission at week 12 [i]	9%	24%	15% [9%, 21%][a]	4%	19%	15% [9%, 21%][a]

[a] Statistically significant under multiplicity control for risankizumab vs placebo comparison ($p < 0.001$).
[b] Statistically significant under multiplicity control for risankizumab vs placebo comparison ($p \leq 0.01$).
c Nominal $p \leq 0.05$ risankizumab vs placebo comparison.
d Adjusted treatment difference.
e Clinical remission based on SF/APS: average daily SF ≤2.8 and not worse than baseline and average daily AP score ≤1 and not worse than baseline.
f Endoscopic response: greater than 50% decrease in SES-CD from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease
g Enhanced SF/APS clinical response: ≥60% decrease in average daily SF and/or ≥35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission.
h Mucosal healing: SES-CD ulcerated surface subscore of 0 in subjects with a subscore of ≥1 at Baseline.
i Endoscopic remission: SES-CD ≤4 and at least a 2 point reduction versus Baseline and no subscore greater than 1 in any individual variable.

At week 12, a higher proportion of subjects treated with risankizumab achieved a decrease of at least 100 points in baseline CDAI compared to placebo (ADVANCE, risankizumab =60%, placebo=37%, p<0.001; MOTIVATE, risankizumab =60%, placebo=30%, p<0.001).

At week 12, a higher proportion of subjects treated with risankizumab achieved both enhanced SF/APS clinical response and endoscopic response at week 12 compared to placebo (ADVANCE, risankizumab =31%, placebo=8%, p<0.001; MOTIVATE, risankizumab =21%, placebo=7% p<0.001).

The results for the co-primary endpoints for the subgroups (without allowing for multiplicity) of subjects with and without prior biologic failure are presented in Table 10.

Table 10. Efficacy Results at week 12 in subgroups of subjects with prior biologic failure and subjects without prior biologic failure in ADVANCE

	ADVANCE		
	Placebo IV	**risankizumab 600 mg**	**Treatment difference (95% CI)**
Clinical Remission per SF/AP Score			
Prior biologic failure	23% (N=97)	41% (N=195)	18% [7%, 29%]
Without prior biologic failure	21% (N=78)	48% (N=141)	27% [15%, 39%]
Endoscopic Response			
Prior biologic failure	11% (N=97)	33% (N=195)	21% [12%, 31%]
Without prior biologic failure	13% (N=78)	50% (N=141)	38% [27%, 49%]

In ADVANCE, a higher proportion of subjects treated with risankizumab with and without prior biologic failure achieved CDAI < 150 compared to placebo (With prior biologic failure, risankizumab = 42%, placebo = 26%; Without prior biologic failure, risankizumab = 49%, placebo = 23%).

CD-related hospitalisations
Rates of CD-related hospitalisations through week 12 were lower in subjects treated with risankizumab compared to placebo (ADVANCE, risankizumab =3%, placebo=12%, p<0.001; MOTIVATE, risankizumab =3%, placebo=11%, p≤0.01).

FORTIFY

The maintenance study FORTIFY evaluated 462 subjects with SF/APS clinical response to 12 weeks of risankizumab IV induction treatment in studies ADVANCE and MOTIVIATE. Subjects were randomized to continue to receive a maintenance regimen of risankizumab 360 mg SC (recommended dose), or risankizumab 180 mg SC every 8 weeks, or to withdraw from risankizumab induction and receive placebo SC every 8 weeks for up to 52 weeks.

The co-primary endpoints were clinical remission at week 52 and, endoscopic response at week 52. Co-primary endpoints were also measured in subjects with and without prior biologic failure (Table 11).

Table 11. Efficacy Results in FORTIFY at week 52 (64 weeks from initiation of risankizumab induction dose)

	FORTIFY		
	risankizumab IV Induction/ Placebo SC[f] (N=164) %	**risankizumab IV Induction/ risankizumab 360 mg SC (N=141) %**	**Treatment difference (95% CI)**
Co-primary endpoints			
Clinical Remission	40%	52%	15% [5%, 25%][a,g]
Prior biologic failure	34% (N=123)	48% (N=102)	14% [1%,27%]
Without prior biologic failure	56% (N=41)	62% (N=39)	5% [-16%,27%]
Endoscopic Response	22%	47%[c]	28% [19%, 37%][b,g]
Prior biologic failure	20% (N=123)	44% (N=102)	23% [11%, 35%]
Without prior biologic failure	27% (N=41)	54% (N=39)	27% [6%, 48%]
Additional endpoints			

Enhanced SF/APS Clinical Response	49%	59%	13% [2%, 23%][e,g]
Maintenance of Clinical Remission[h]	51% (N=91)	69% (N=72)	21% [6%, 35%][d,g]
Endoscopic Remission	13%	39%	28% [20%, 37%][c,g]
Mucosal Healing	10% (N=162)	31% (N=141)	22% [14%, 30%][c,g]

[a] Statistically significant under multiplicity control for risankizumab vs placebo comparison ($p \leq 0.01$).
[b] Statistically significant under multiplicity control for risankizumab vs placebo comparison ($p < 0.001$).
[c] Nominal $p < 0.001$ risankizumab vs placebo comparison without overall type I error control.
[d] Nominal $p \leq 0.01$ risankizumab vs placebo comparison without overall type I error control.
[e] Nominal $p \leq 0.05$ risankizumab vs placebo comparison without overall type I error control.
[f] The induction-only group consisted of subjects who achieved clinical response to risankizumab induction therapy and were randomized to receive placebo in the maintenance study (FORTIFY).
[g] Adjusted treatment difference.
[h] Maintenance of clinical remission: clinical remission at week 52 in subjects with clinical remission at week 0.

Deep remission at week 52 was observed at higher rates in subjects treated with risankizumab IV/ risankizumab SC compared to subjects who received risankizumab IV/placebo SC (28% vs. 10%, respectively, $p < 0.001$).

At week 52, a higher proportion of subjects treated with risankizumab IV/ risankizumab SC achieved CDAI < 150 compared to risankizumab IV/placebo SC (52% vs. 41%, respectively, $p \leq 0.01$). A higher proportion of subjects treated with risankizumab IV/ risankizumab SC achieved a decrease of at least 100 points in baseline CDAI score compared to subjects treated with risankizumab IV/placebo SC (62% vs. 48%, respectively, $p \leq 0.01$).

91 subjects who did not demonstrate SF/APS clinical response 12 weeks after risankizumab induction in studies ADVANCE and MOTIVATE received subcutaneous 360 mg dose of risankizumab at week 12 and week 20. Of these subjects, 64% (58/91) achieved SF/APS clinical response at week 24; 33 of the subjects achieving SF/APS clinical response enrolled in FORTIFY and continued receiving risankizumab 360 mg SC every 8 weeks for up to 52 weeks. Among these subjects, 55% (18/33) achieved clinical remission and 45% (15/33) achieved endoscopic response at week 52.

During FORTIFY, 30 subjects had loss of response to risankizumab 360 mg SC treatment and received rescue treatment with risankizumab (1200 mg IV single dose, followed by 360 mg SC every 8 weeks). Of these subjects, 57% (17/30) achieved SF/APS clinical response at week 52. In addition, 20% (6/30) and 34% (10/29) of subjects achieved clinical remission and endoscopic response at week 52, respectively.

Secondary endpoints measured at week 52 included enhanced SF/APS clinical response, maintenance of clinical remission (clinical remission at week 52 in subjects with clinical remission at week 0), mucosal healing, endoscopic remission, deep remission (clinical remission and endoscopic remission), and CDAI < 150.

Risankizumab has been shown to improve signs and symptoms and health related quality of life, as well as decrease mucosal inflammation as measured by endoscopy.

Health-related and quality of life outcomes

Health-related quality of life was assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ), 36-Item Short Form Health Survey (SF-36), and the European Quality of Life 5 Dimensions (EQ-5D). Improvement in fatigue was evaluated by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale. Work productivity was assessed by the Work Productivity and Activity Impairment CD (WPAI-CD) Questionnaire.

At week 12 of ADVANCE and MOTIVATE, subjects treated with risankizumab achieved clinically meaningful improvements from baseline in IBDQ total score, all IBDQ domain scores (bowel symptoms, systemic function, emotional function, and social function), SF-36 Physical and Mental Component Summary Score, EQ-5D VAS, and FACIT-Fatigue compared to placebo. For WPAI-CD greater reductions in impairment while working, overall work impairment, and activity impairment were demonstrated in ADVANCE; and greater reduction in activity impairment was demonstrated in MOTIVATE. These improvements were maintained in subjects treated with risankizumab IV/ risankizumab SC in FORTIFY through week 52.

Pharmacokinetic properties

The pharmacokinetics of risankizumab was similar between subjects with plaque psoriasis, psoriatic arthritis and palmoplantar pustulosis.

Absorption

Risankizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure across dose ranges of 18 to 360 mg and 0.25 to 1 mg/kg administered subcutaneously, and 200 to 1,800 mg and 0.01 to 5 mg/kg administered intravenously.

Following subcutaneous dosing of risankizumab, peak plasma concentrations were achieved between 3-14 days after dosing with an estimated absolute bioavailability of 74%-89%. With dosing of 150 mg at week 0, week 4 and every 12 weeks thereafter, estimated steady-state peak and trough plasma concentrations are 12 and 2 µg/mL, respectively.

In subjects with Crohn's disease treated with 600 mg IV induction dose at weeks 0, 4, and 8 followed by 360 mg SC maintenance dose at week 12 and every 8 weeks thereafter, maximum median peak and trough concentrations are estimated to be 156 and 38.8 µg/mL respectively during the induction period (weeks 8-12) and steady state median peak and trough concentrations are estimated to be 28.0 and 8.13 ug/mL respectively during the maintenance period (weeks 40-48).

Bioequivalence was demonstrated between a single risankizumab 150 mg/ml injection and two risankizumab 75 mg/0.83ml injections in pre-filled syringe. Bioequivalence was also demonstrated between risankizumab 150 mg/ml pre-filled syringe and pre-filled pen.

Distribution

The mean (±standard deviation) steady-state volume of distribution (V_{ss}) of risankizumab was 11.4 (±2.7) L in Phase 3 studies in subjects with psoriasis, indicating that the distribution of risankizumab is primarily confined to the vascular and interstitial spaces.

In a typical 90 kg subject with psoriasis, the steady-state volume of distribution (V_{ss}) was 11.2 L, indicating that the distribution of risankizumab is primarily confined to the vascular and interstitial spaces. In a typical 70 kg subject with Crohn's disease, V_{ss} was 7.68 L.

Biotransformation

Therapeutic IgG monoclonal antibodies are typically degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. Risankizumab is not expected to be metabolised by cytochrome P450 enzymes.

Elimination

The mean (±standard deviation) systemic clearance (CL) of risankizumab was 0.3 (±0.1) L/day in Phase 3 studies in subjects with psoriasis. The mean terminal elimination half-life of risankizumab ranged from 28 to 29 days in Phase 3 studies in subjects with psoriasis. For a typical 70 kg subject with Crohn's disease, CL was 0.30 L/day and terminal elimination half-life was 21 days.

As an IgG1 monoclonal antibody, risankizumab is not expected to be filtered by glomerular filtration in the kidneys or to be excreted as an intact molecule in the urine.

Linearity/non-linearity

Risankizumab exhibited linear pharmacokinetics with approximately dose-proportional increases in systemic exposure (C_{max} and AUC) in the evaluated dose ranges of 18 to 300 mg or 0.25 to 1 mg/kg subcutaneous administration in healthy subjects or subjects with psoriasis or Crohn's disease.

Interactions

Interaction studies were conducted in subjects with plaque psoriasis or Crohn's disease to assess the effect of repeated administration of risankizumab on the pharmacokinetics of cytochrome P450 (CYP) sensitive probe substrates. The exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate) and midazolam (CYP3A substrate) following risankizumab treatment were comparable to their exposures prior to risankizumab treatment, indicating no clinically meaningful drug interactions through these enzymes.

Population pharmacokinetic analyses indicated that risankizumab exposure was not impacted by concomitant medicinal products (metformin, atorvastatin, lisinopril, amlodipine, ibuprofen, acetylsalicylate and levothyroxine) used by some subjects with plaque psoriasis during the clinical studies. Similar lack of impact was observed based on population pharmacokinetic analyses in psoriatic arthritis and Crohn's disease.

Special populations

Paediatric population

The pharmacokinetics of risankizumab in paediatric subjects under 16 years of age has not been established. Risankizumab exposures in 16- to 17-year-old subjects with Crohn's disease were similar to those in adults. Age was not found to have any significant impact on risankizumab exposure based on the population pharmacokinetic analyses.

Elderly patients

Of the 2,234 subjects with plaque psoriasis exposed to risankizumab, 243 were 65 years or older and 24 subjects were 75 years or older. Of the 1574 subjects with Crohn's disease exposed to risankizumab, 72 were 65 years or older and 5 subjects were 75 years or older. No overall differences in risankizumab exposure were observed between older and younger subjects who received risankizumab.

Patients with renal or hepatic impairment

No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of risankizumab. Based on population pharmacokinetic analyses, serum creatinine levels, creatinine clearance, or hepatic function markers (ALT/AST/bilirubin) did not have a meaningful impact on risankizumab clearance in subjects with psoriasis, psoriatic arthritis, or Crohn's disease.

As an IgG1 monoclonal antibody, risankizumab is mainly eliminated via intracellular catabolism and is not expected to undergo metabolism via hepatic cytochrome P450 enzymes or renal elimination.

Body weight

Risankizumab clearance and volume of distribution increase as body weight increases which may result in reduced efficacy in subjects with high body weight (>130 kg). However, this observation is based on a limited number of subjects. No dose adjustment based on body weight is currently recommended.

Gender or race

The clearance of risankizumab was not significantly influenced by gender or race in adult subjects with plaque psoriasis, psoriatic arthritis, or Crohn's disease. No clinically meaningful differences in risankizumab exposure were observed in Chinese or Japanese subjects compared to Caucasian subjects in a clinical pharmacokinetic studies in healthy volunteers.

Preclinical safety data

Nonclinical data revealed no special hazard for humans based on repeat-dose toxicity studies including safety pharmacology evaluations, and an enhanced pre- and post-natal developmental toxicity study in cynomolgus monkeys at doses of up to 50 mg/kg/week (producing exposures of ≥70 times the clinical exposure at the MRHD for psoriasis and psoriatic arthritis (150 mg SC). For Crohn's disease, these doses produced exposures 10 times the clinical exposures during induction at a dose of 600 mg IV every 4 weeks and 39 times the clinical exposures for maintenance when given 360 mg SC every 8 weeks.

Mutagenicity and carcinogenicity studies have not been conducted with risankizumab. In a 26-week chronic toxicology study in cynomolgus monkeys at doses of up to 50 mg/kg/week (about 70 times the clinical exposure at the MRHD for psoriasis and psoriatic arthritis), there were no pre-neoplastic or neoplastic lesions observed and no adverse immunotoxicity or cardiovascular effects were noted. For Crohn's disease, these doses in the 26-week chronic study in cynomolgus monkeys produced exposures 7 times the clinical exposures during induction at a dose of 600 mg IV every 4 weeks and 28 times the clinical exposures for maintenance when given 360 mg SC every 8 weeks.

PHARMACEUTICAL PARTICULARS

List of excipients

Skyrizi 150 mg solution for injection in pre-filled pen and pre-filled syringe

Sodium acetate trihydrate
Acetic acid
Trehalose dihydrate
Polysorbate 20
Water for injections

Skyrizi Solution for Injection in Pre-filled Cartridge 360mg/2.4mL

acetic acid,
polysorbate 20
sodium acetate trihydrate
trehalose dihydrate
water for injection

Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only).

acetic acid
polysorbate 20
sodium acetate trihydrate
trehalose dihydrate
water for injection.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

2 years

Diluted solution for intravenous infusion (Skyrizi Concentrate for Solution for Infusion 600mg/10mL)

Chemical and physical in-use stability has been demonstrated for 20 hours at 2°C to 8°C (protected from light) or up to 8 hours at room temperature (protected from sunlight). Storage time at room temperature begins once the diluted solution has been prepared. The infusion should be completed within 8 hours after dilution in the infusion bag. Exposure to indoor light is acceptable during room temperature storage and administration.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and should not be longer than 20 hours at 2°C to 8°C.

Do not freeze.

Special precautions for storage

Skyrizi 150 mg Solution for Injection in Pre-filled Pen and Pre-filled Syringe and Skyrizi Solution for Injection in Pre-filled Cartridge 360mg/2.4mL

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the pre-filled pen, the pre-filled syringe(s) or cartridge in the outer carton in order to protect from light.

Skyrizi 150 mg/mL prefilled pen or prefilled syringe and Skyrizi Solution for Injection in Pre-filled Cartridge with On-body Injector 360mg/2.4mL may be stored out of the refrigerator (up to a maximum of 25°C (77°F)) for up to 24 hours in the original carton to protect from light.

Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only)

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see **Shelf life** section.

Nature and contents of container

Skyrizi 150 mg solution for injection in pre-filled pen

Pre-filled glass syringe assembled in a pre-filled pen with an automatic needle sleeve.

Skyrizi 150 mg solution for injection in pre-filled syringe

Pre-filled glass syringe with a fixed needle and needle cover, assembled in an automatic needle guard.

Skyrizi 150 mg is available in packs containing 1 pre-filled pen or 1 pre-filled syringe.

Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only)

Each carton contains 1 vial.

Skyrizi Solution for Injection in Pre-filled Cartridge with On-body Injector 360mg/2.4mL

Each carton contains 1 prefilled cartridge with 1 on body injector.

Not all presentations may be marketed.

Special precautions for disposal and other handling

Skyrizi 150 mg solution for injection in pre-filled pen

Before injecting, patients should remove the carton from the refrigerator and allow to reach room temperature out of direct sunlight (30 to 90 minutes) without removing the pre-filled pen from the carton.

The solution should be colourless to yellow and clear to slightly opalescent.

Skyrizi 150 mg solution for injection in pre-filled syringe

Before injecting, patients may remove the carton from the refrigerator and allow to reach room temperature out of direct sunlight (15 to 30 minutes) without removing the pre-filled syringe from the carton.

The solution should be colourless to yellow and clear to slightly opalescent.

General special precautions

Prior to use, a visual inspection of each pre-filled pen or pre-filled syringe is recommended. The solution may contain a few translucent to white product-related particles. Skyrizi should not be used if the solution is cloudy or discoloured, or contains large particles. Do not shake the pre-filled pen or pre-filled syringe.

Comprehensive instructions for use are provided in the package leaflet.

Each pre-filled pen or pre-filled syringe is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Skyrizi Concentrate for Solution for Infusion 600mg/10mL (intravenous infusion only)

The solution in the vial and dilutions should not be shaken. The solutions should be visually inspected for particulate matter or discoloration prior to administration. The solution should be colourless to slightly yellow and clear to slightly opalescent. The liquid may contain tiny white or clear particles. The medicinal product and its dilutions should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

Skyrizi Solution for Injection in Pre-filled Cartridge with On-body Injector 360mg/2.4mL

Skyrizi is intended for use under the guidance and supervision of a healthcare professional.

Prior to use, a visual inspection of the cartridge is recommended. The solution is free from foreign particles and practically free from product-related particles. Skyrizi should not be used if the solution is cloudy or discoloured, or contains large particles.

The solution should be colourless to yellow and clear to slightly opalescent.

Before injecting, patients should remove the carton from the refrigerator and allow to reach room temperature, out of direct sunlight, for 45 to 90 minutes without removing the cartridge from the carton.

Each on-body injector with cartridge is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MARKETING AUTHORISATION HOLDER

AbbVie Sdn Bhd
Level 9 Menara Lien Hoe
No.8 Persiaran Tropicana
Tropicana Golf & Country Resort
47410 Petaling Jaya, Selangor Darul Ehsan.
MALAYSIA

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