1. 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

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

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody produced in Chinese Hamster Ovary cells using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Skyrizi 150 mg solution for injection in pre-filled pen and in pre-filled syringe
The solution is colourless to yellow and clear to slightly opalescent

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

This medicinal product 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

The recommended dose is 150 mg administered as a subcutaneous injection at week 0, week 4, and every 12 weeks thereafter (150 mg pre-filled pen or pre-filled syringe injection).

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

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

No dose adjustment is required (see section 5.2).
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 section 5.2).

Paediatric population

The safety and efficacy of risankizumab in children and adolescents aged 5 to less than 18 years have not 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.

Overweight patients

No dose adjustment is required (see section 5.2).

Method of administration

Skyrizi is administered by subcutaneous injection.

The injection should be administered in the thigh or abdomen. Patients should not inject into areas where the skin is tender, bruised, erythematous, indurated, or affected by psoriasis.

Patients may self-inject Skyrizi after training in subcutaneous injection technique. Patients should be instructed to read the 'Instructions for use' provided in the package leaflet before administration.

Administration of Skyrizi in the upper, outer arm may only be performed by a healthcare professional or caregiver.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 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 section 5.2).

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of risankizumab (see section 4.8). 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 or 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’.

4.5 Interaction with other medicinal products and other forms of interaction

Risankizumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. Interactions between risankizumab and inhibitors, inducers, or substrates of medicinal product metabolising enzymes are not expected, and no dose adjustment is needed (see section 5.2).

Concomitant immunosuppressive therapy or phototherapy

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

4.6 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were upper respiratory infections (13.0% in psoriasis).

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); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
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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
[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

Description of selected adverse reactions

Infections

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 section 4.4).

Immunogenicity

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 groups 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.

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.

Elderly

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

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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. 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.

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). 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. Patients who completed these studies and other Phase 2/3 studies had the opportunity to enrol in an open-label extension study, LIMMITLESS.

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)	--

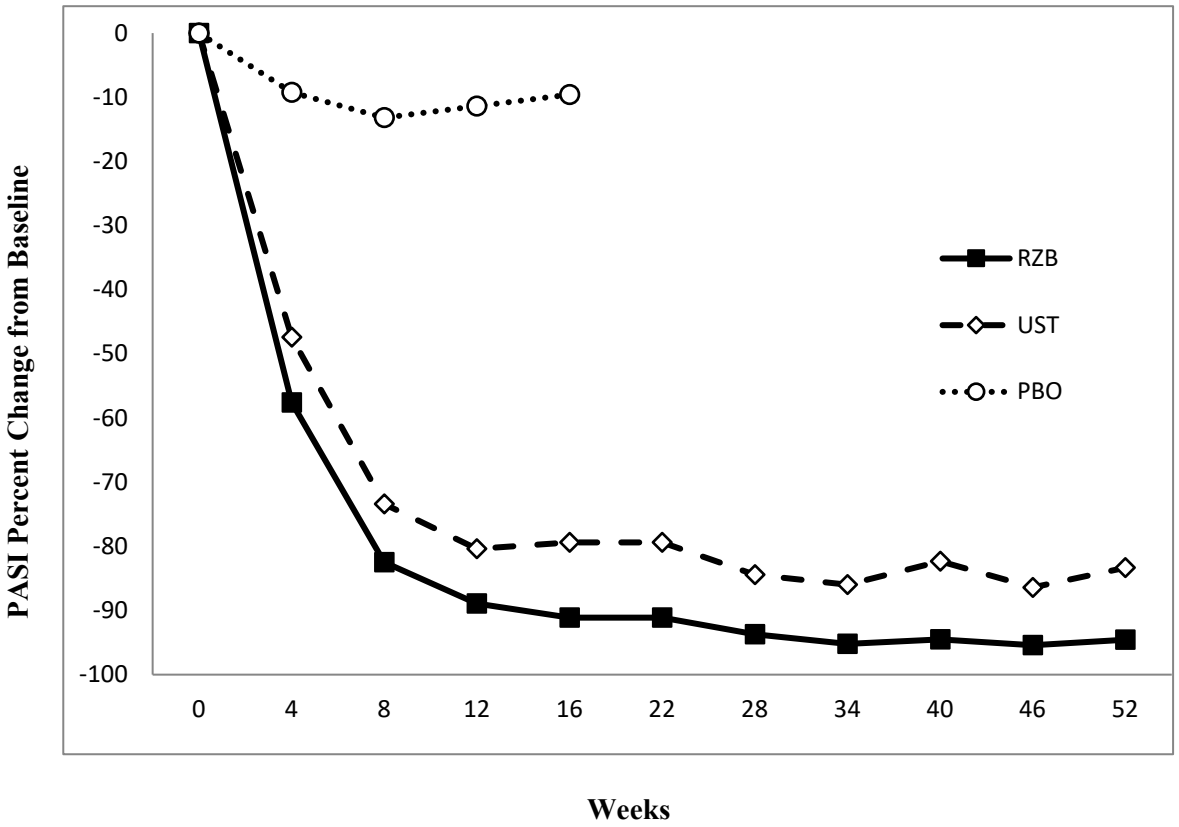
All comparisons of risankizumab versus ustekinumab and placebo achieved $p<0.001$ except for PASI 75 at week 52 in ULTIMMA-2 where $p=0.001$

[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 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						

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

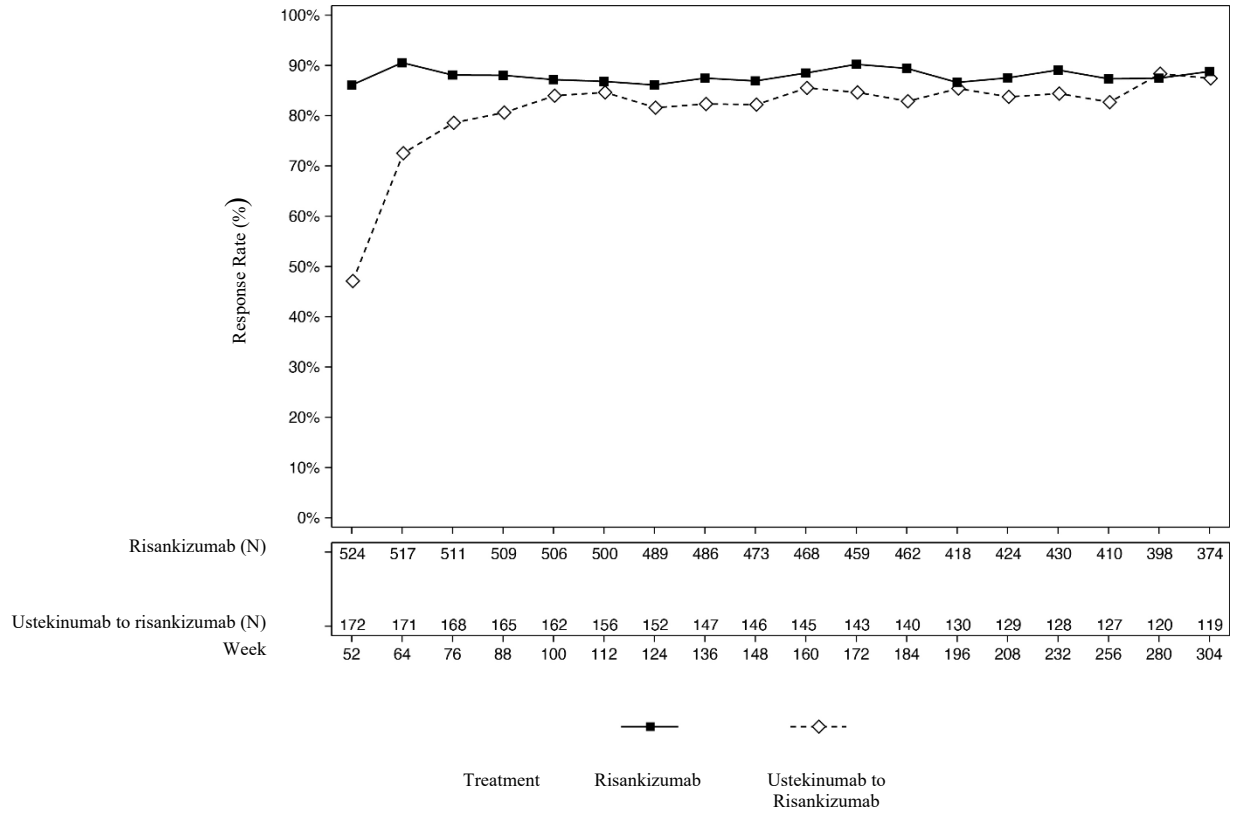
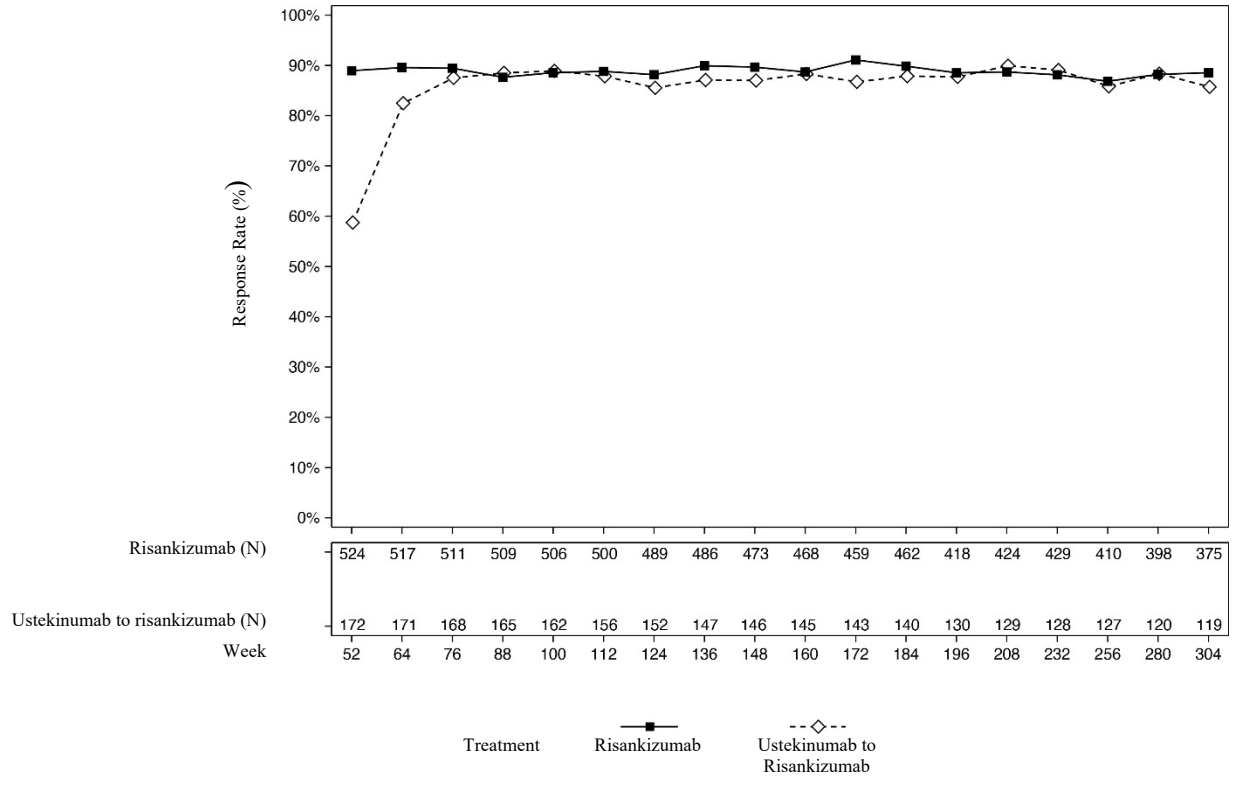


Figure 3: Percent of subjects who achieved an sPGA clear or almost clear response by visit (OC) in LIMMITLESS



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. Subjects who were originally on risankizumab and had a sPGA of clear or almost clear at week 28 were re-randomised to continue risankizumab every 12 weeks through week 88 (with follow-up 16 weeks after last risankizumab dose) or have treatment withdrawn.

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		

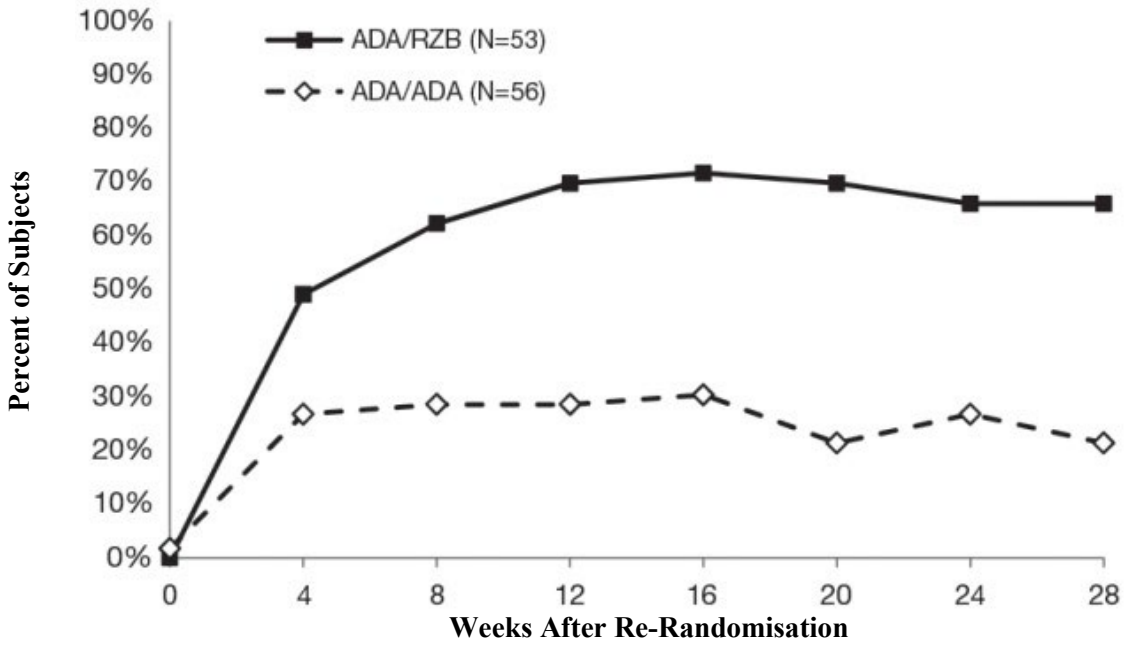
For subjects who had PASI 50 to <PASI 90 with adalimumab at week 16 and were re-randomised, differences in PASI 90 response rates between switching to risankizumab and continuing adalimumab were noted 4 weeks after re-randomisation (49.1% vs 26.8%, respectively).

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 washout 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 1 407 subjects with active PsA in 2 randomised, 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 randomised 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]

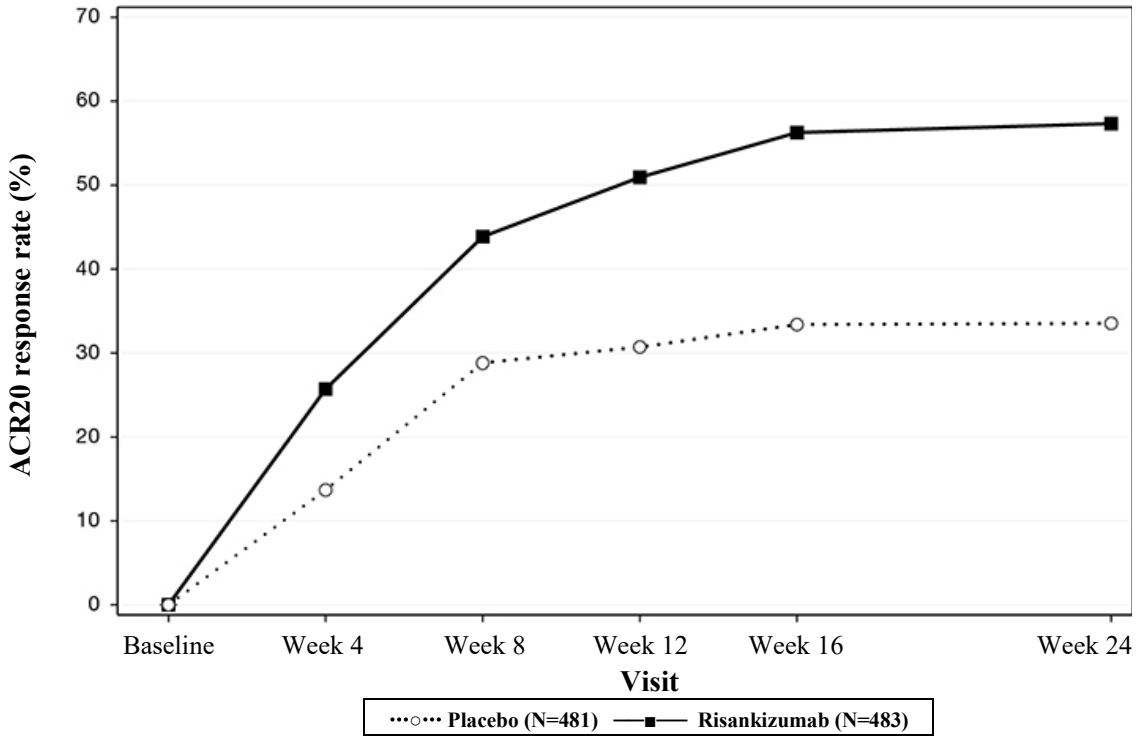
Week 52*	-	125/437 (28.6)	-	37/192 (19.3)
Resolution of Enthesitis (LEI=0)				
Week 24*	156/448 (34.8) [d]	215/444 (48.4) [a, d]	-	-
Week 52*	-	244/393 (62.1) [d]	-	-
Resolution of Dactylitis (LDI=0)				
Week 24*	104/204 (51.0) [e]	128/188 (68.1) [a, e]	-	-
Week 52*	-	143/171 (83.6) [e]	-	-
Minimal Disease 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 PsA.

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 PsA 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 $\leq$ 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.

5.2 Pharmacokinetic properties

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

Absorption

Risankizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure across dose ranges of 18 to 300 mg and 0.25 to 1 mg/kg administered subcutaneously, and 200 to 1,200 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 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.

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

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.

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.

Interactions

An interaction study was conducted in subjects with plaque psoriasis 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 interactions through these enzymes.

Population pharmacokinetic analyses indicated that risankizumab exposure was not impacted by concomitant treatment used by some subjects with plaque psoriasis or psoriatic arthritis during the clinical studies.

Special populations

Paediatric population

The pharmacokinetics of risankizumab in paediatric subjects has not been established.

Elderly

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 1 542 subjects with psoriatic arthritis exposed to risankizumab, 246 were 65 years or older and 34 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 plaque psoriasis or psoriatic arthritis.

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 or psoriatic arthritis. No clinically meaningful differences in risankizumab exposure were observed in Chinese or Japanese subjects compared to Caucasian subjects in a clinical pharmacokinetic study in healthy volunteers.

5.3 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 about 70 times the clinical exposure at maximum recommended human dose [MRHD]).
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), there were no pre-neoplastic or neoplastic lesions observed and no adverse immunotoxicity or cardiovascular effects were noted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Trehalose dihydrate
Sodium acetate trihydrate
Polysorbate 20
Acetic acid, glacial
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

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

Skyrizi 150 mg pre-filled pen or pre-filled syringe may be stored out of the refrigerator (up to a maximum of 25°C) for up to 24 hours in the original carton to protect from light.

6.5 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.

Not all presentations may be marketed.

6.6 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.

7. MANUFACTURER

AbbVie Deutschland GmbH & Co. KG, Knollstrasse 67061 Ludwigshafen, Germany.

8. LICENSE HOLDER

AbbVie biopharmaceuticals LTD., 4 Haharash., Hod Hasharon, Israel.

9. REGISTRATION NUMBER

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