Summary Report of Benefit-Risk Assessment

SKYRIZI SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 75MG

NEW DRUG APPLICATION

Active Ingredient(s)	Risankizumab
Product Registrant	Abbvie Pte Ltd
Product Registration Number	SIN15972P
Application Route	Abridged evaluation
Date of Approval	06 July 2020

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A INTRODUCTION

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

The active substance, risankizumab, selectively binds to the p19 subunit of human interleukin 23 (IL-23), thereby inhibiting the action of IL-23 to induce and sustain T helper (Th) 17 type cells, innate lymphoid cells, γδT cells, and natural killer (NK) cells responsible for tissue inflammation, destruction and aberrant tissue repair. Excessive expression of IL-23 has been reported in affected skin in psoriasis and IL-23 may be disproportionately involved in the maintenance of chronic psoriasis.

Skyrizi Solution for Injection in Pre-filled Syringe 75 mg/0.83 mL is available as an injection solution containing 75 mg/0.83mL of risankizumab. Other ingredients in the prefilled syringe are disodium succinate hexahydrate, succinic acid, sorbitol, polysorbate 20 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, risankizumab, is manufactured at Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Riss, Germany. The drug product, Skyrizi, is manufactured at Boehringer Ingelheim Pharma GmbH & KG, Biberach an der Riss, Germany and packed at Abbvie S.r.l, Compoverde di Aprilia, Italy.

Drug substance:
Adequate controls have been presented for the starting materials, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on [redacted] consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Product related and process related impurities are adequately controlled. The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Riss, Germany is adequate to support the approved storage condition and shelf life. [redacted]

Drug product:
The manufacturing process utilises aseptic processing. The process is considered to be a standard process.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted is adequate to support the approved shelf-life of 24 months when stored at 2-8ºC. The container closure system is a 1 mL [redacted] glass syringe with a staked-in 29G needle, [redacted] rubber stopper and rigid needle shield. Each carton contains two prefilled syringes and two alcohol pads.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of risankizumab in the treatment of moderate to severe plaque psoriasis was based primarily on four pivotal Phase III studies, namely ULTIMMA-1, ULTIMMA-2, IMMvent and IMMhance. These were all multicentre, randomised, double-blind controlled parallel studies of risankizumab compared with placebo or active comparators in adult patients with stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis and who were candidates for systemic therapy or phototherapy.

ULTIMMA-1 and ULTIMMA-2 were identically designed studies which compared risankizumab to placebo and ustekinumab in the target patient population. In the first 16 weeks of the study (Part A), patients were randomised in a 3:1:1 ratio to receive subcutaneous doses of risankizumab 150 mg, ustekinumab 45 mg or 90 mg (based on body weight at screening) or placebo at Weeks 0, 4 and 16. In Part B of the study (up to Week 52), patients who received placebo in Part A were switched to risankizumab 150 mg at Week 16, while other patients continued on the treatments given in Part A. Study treatments were administered every 12 weeks in Part B. Ustekinumab is an established treatment option for the treatment of moderate to severe plaque psoriasis and is approved in Singapore for this use, hence the use of ustekinumab as an active comparator is considered acceptable.

The co-primary efficacy endpoints were PASI 90 response and sPGA score of clear or almost clear at Week 16 (risankizumab vs placebo). Key secondary efficacy endpoints were PASI 100 response, sPGA clear, Psoriasis Symptom Scale (PSS) outcomes and quality of life scores (Dermatology Life Quality Index DLQI) at Week 16, and PASI 90 and PASI 100 responses at Week 52. Comparisons between risankizumab and ustekinumab were included as secondary efficacy endpoints up to Week 52.

In ULTIMMA-1, 506 patients were randomised and included in the ITT and safety populations in Part A – 304 to risankizumab, 100 to ustekinumab and 102 to placebo treatment. Similarly, in ULTIMMA-2, 491 patients were randomised and included in the ITT and safety populations in Part A – 294 to risankizumab, 99 to ustekinumab and 98 to placebo treatment.

Demographics and baseline disease characteristics were similar between the treatment arms in both studies. The majority of patients were male (approximately 70%) and White, although ULTIMMA-1 had more Asian patients than ULTIMMA-2 (26.9% vs 7.3%, respectively). Most patients fell within the 40-<65 years age category in both studies. The baseline disease characteristics confirmed that the study population had moderate to severe plaque psoriasis – the average PASI response at baseline was 20.49 ± 7.312 (range: 12.0-54.7) and 19.73 ± 7.423 (range: 12.0-60.3) in ULTIMMA-1 and ULTIMMA-2, respectively, while the mean BSA

involvement was 26.3% and 24.7%, respectively. Around half of the patients in both studies had previously received non-biologic systemic therapy and 21.3% and 23.8% of patients had prior exposure to TNF antagonists in ULTIMMA-1 and ULTIMMA-2, respectively.

In both studies, risankizumab was shown to be superior to placebo in terms of PASI 90 and sPGA clear/almost clear at Week 16. The adjusted difference in PASI 90 response was 70.3% (95%CI 64.0%, 76.7%; p<0.0001) in ULTIMMA-1 and 72.5% (95%CI 66.8%, 78.2%; p<0.0001) in ULTIMMA-2. The adjusted difference in sPGA clear/almost clear was 79.9% (95%CI 73.5%, 86.3%; p<0.0001) in ULTIMMA-1 and 78.5% (95%CI 72.4%, 84.5%; p<0.0001) in ULTIMMA-2. The primary efficacy results were consistent in various sensitivity analyses based on different subgroups, demonstrating robustness of the data.

Risankizumab was also superior to ustekinumab at Week 16 for all key secondary endpoints, including quality of life and PSS total score. The adjusted difference in PASI 90 response was 33.5% (95%CI 22.7%, 44.3%; p<0.0001) in ULTIMMA-1 and 27.6% (95%CI 16.7%, 38.5%; p<0.0001) in ULTIMMA-2. The adjusted difference in sPGA clear/almost clear was 25.1% (95%CI 15.2%, 35.0%; p<0.0001) in ULTIMMA-1 and 22.3% (95%CI 12.0%, 32.5%; p<0.0001) in ULTIMMA-2. The benefit of risankizumab over ustekinumab was similarly demonstrated for the more stringent parameters of PASI 100 response and sPGA clear and these effects were maintained up to Week 52.

Summary of Key Efficacy Results (ULTIMMA-1, ULTIMMA-2)

	ULTIMMA-1		**ULTIMMA-2**	
	PBO N = 102	**RZB N = 304**	**PBO N = 98**	**RZB N = 294**
Co-primary endpoints				
PASI 90 at Week 16				
n (%)	5 (4.9)	229 (75.3)	2 (2.0)	220 (74.8)
Adjusted Difference	70.3%		72.5	
95% CI	64.0. 76.7		66.8, 78.2	
p-value	<0.0001		<0.0001	
sPGA clear/almost clear at Week 16				
n (%)	9 (7.8)	267 (87.8)	5 (5.1)	246 (83.7)
Adjusted Difference	79.9%		78.5	
95% CI	73.5, 86.3		72.4, 84.5	
p-value	<0.0001		<0.0001	
Key Secondary Endpoints				
sPGA clear at Week 16				
n (%)	2 (2.0)	112 (36.8)	3 (3.1)	150 (51.0)
p-value	<0.0001		<0.0001	
PASI 100 at Week 16				
n (%)	0	109 (35.9)	2 (2.0)	149 (50.7)
p-value	<0.0001		<0.0001	
DLQI 0/1 at Week 16				
n (%)	8 (7.8)	200 (65.8)	4 (4.1)	196 (66.7)
p-value	<0.0001		<0.0001	
PSS 0 at Week 16				
n (%)	2 (2.0)	89 (29.3)	0	92 (31.3)
p-value	<0.0001		<0.0001	
	ULTIMMA-1		**ULTIMMA-2**	
	UST N = 100	**RZB N = 304**	**UST N = 99**	**RZB N = 294**
PASI 90 at Week 16				
n (%)	42 (42.0)	299 (75.3)	47 (47.5)	220 (74.8)
p-value	<0.0001		<0.0001	
sPGA clear/almost clear at Week 16				

n (%)	63 (63.0)	267 (87.8)	61 (61.6)	246 (83.7)
p-value	<0.0001		<0.0001	
sPGA clear at Week 16				
n (%)	14 (14.0)	112 (36.8)	25 (25.3)	150 (51.0)
p-value	<0.0001		<0.0001	
PASI 100 at Week 16				
n (%)	12 (12.0)	109 (35.9)	24 (24.2)	149 (50.7)
p-value	<0.0001		<0.0001	
DLQI 0/1 at Week 16				
n (%)	43 (43.0)	200 (65.8)	46 (46.5)	196 (66.7)
p-value	<0.0001		<0.0001	
PASI 90 at Week 52				
n (%)	44 (44.0)	249 (81.9)	50 (50.5)	237 (80.6)
p-value	<0.0001		<0.0001	
PASI 100 at Week 52				
n (%)	21 (21.0)	171 (56.3)	30 (30.3)	175 (59.5)
p-value	<0.0001		<0.0001	

PBO: placebo; RZB: risankizumab; UST: ustekinumab

The IMMvent study compared risankizumab to adalimumab in the target patient population, including those who switched treatment from adalimumab to risankizumab. In the first 16 weeks of the study (Part A), patients were randomised in a 1:1 ratio to receive either risankizumab (150 mg at Weeks 0, 4 and 16) or adalimumab (80 mg loading dose at Week 0, then 40 mg every 2 weeks). In Part B (up to Week 44), patients who received risankizumab in Part A continued to do so in Part B. Patients well-controlled on adalimumab (>PASI 90 response) continued with adalimumab treatment. Patients who were on adalimumab in Part A but not responding (<PASI 50 response) were switched to risankizumab in Part B. All other patients on adalimumab in Part A (> PASI 50 and < PASI 90) were re-randomised in a 1:1 ratio to receive either risankizumab 150 mg or adalimumab 40 mg.

The endpoints studied in IMMvent were generally similar to those in ULTIMMA-1 and ULTIMMA-2. The co-primary efficacy endpoints were PASI-90 response and sPGA score of clear or almost clear at Week 16 (risankizumab vs adalimumab). The key secondary endpoints were PASI 75 and PASI 100 response at Week 16. Additionally, the primary and key secondary endpoints for Part B were PASI 90 and PASI 100 response at Week 44, respectively (for patients re-randomised at Week 16).

A total of 605 patients were randomised and included in the ITT and safety populations in Part A (risankzumab: 301; adalimumab: 304). 20 subjects discontinued Part A prematurely and 585 patients continued into Part B of the study (continued risankizumab: 294; continued adalimumab: 144; switched to risankizumab: 38; re-randomised: 109 (adalimumab: 56; risankizumab: 53).

Overall demographics were similar between the treatment arms in Parts A and B – the majority of subjects were male and White and most subjects fell within the 40-<65 years age category. Baseline disease characteristics were similar between the treatment arms in Parts A and B, and all had moderate to severe disease as measured by PGA and PASI (all randomised subjects: mean PASI score 19.84 ± 7.48 (range: 12.0-50.4); mean BSA involvement 26.0% ± 16.62% (range: 10-85). The treatment groups were balanced with regard to prior psoriasis medication history. 48.3% of the patients had previously received non-biologic systemic therapy and 14.7% of patients had prior exposure to TNF antagonists.

In Part A, risankizumab was superior to adalimumab in terms of PASI 90 and sPGA clear/almost clear. The adjusted difference in PASI 90 response at Week 16 was 24.9% (95%CI 17.5%, 32.4%; p<0.0001). The adjusted difference in sPGA clear/almost clear was 23.3% (95%CI 16.6%, 30.1%; p<0.0001). The primary efficacy results were consistent in various sensitivity analyses based on different subgroups, demonstrating robustness of the data. In patients who were re-randomised from adalimumab to risankizumab, PASI 90 response was significantly higher than those who were re-randomised to remain on adalimumab – the adjusted difference at Week 44 was 45.0% (95%CI 28.9, 61.1; p<0.0001). A similar outcome was observed in terms of PASI 100 response at Week 44 (adjusted difference 32.8%; p<0.0001).

In Part B, subjects who were non-responders to adalimumab (< PASI 50 at Week 16) received clinical benefit from switching to risankizumab, with >60% achieving PASI 90 and sPGA clear or almost clear at Week 44. On the other hand, subjects who received continuous risankizumab saw persistent or increased responses until the end of the study – 157/301 (52.2%) achieved sPGA clear and 159/301 (52.8%) achieved PASI 100 at Week 44.

Summary of Key Efficacy Results (IMMvent)

Part A		
	ADA N = 304	**RZB N = 301**
Co-primary endpoints		
PASI 90 at Week 16		
n (%)	144 (47.4)	218 (72.4)
Adjusted Difference	24.9%	
95% CI	17.5, 32.4	
p-value	<0.0001	
sPGA clear or almost clear at Week 16		
n (%)	183 (60.2)	252 (83.7)
Adjusted Difference	23.3%	
95% CI	16.6, 30.1	
p-value	<0.0001	
Key Secondary Endpoint		
PASI 75 at Week 16		
n (%)	218 (71.7)	273 (90.7)
Adjusted Difference	18.9%	
p-value	<0.0001	
PASI 100 at Week 16		
n (%)	70 (23.0)	120 (39.9)
Adjusted Difference	16.7%	
p-value	<0.0001	
Part B (re-randomised patients only)		
	ADA/ADA N = 56	**ADA/RZB N = 53**
PASI 90 at Week 44 (re-randomised patients only)		
n (%)	12 (21.4)	35 (66.0)
Adjusted Difference	45.0%	
p-value	<0.0001	

ADA: adalimumab; RZB: risankizumab

The IMMhance study was conducted to study the maintenance of response following risankizumab withdrawal after 28 weeks of treatment, as well as the response after re-treatment in subjects who experienced relapse after drug withdrawal. The study lasted 104 weeks, comprising an 88-week treatment period followed by a 16-week follow-up period. The treatment period was made up of Part A (28 weeks) and Part B (60 weeks). In Part A, patients

were randomised in a 4:1 ratio to receive blinded risakizumab 150 mg at Weeks 0, 4 and 16 or placebo. At Week 16, patients receiving placebo were switched to blinded risankizumab 150 mg.

At Week 28 (Part B), responders (sPGA 0 or 1) who were receiving risankizumab from the beginning of the study were re-randomised to either continue receiving risankizumab or switch to placebo (drug withdrawal). Responders who were initially receiving placebo in Part A were switched to blinded risankizumab, while all non-responders (sPGA ≥2) received open-label risankizumab 150 mg until Week 88. Patients who relapsed on blinded treatment from Week 32 were switched to open-label risankizumab.

As with the previous studies, the co-primary endpoints in Part A were PASI 90 response and sPGA clear or almost clear at Week 16. In Part B, the primary endpoint was sPGA clear or almost clear at Week 52 in patients re-randomised to risankizumab or drug withdrawal. Key secondary endpoints for Part A included PASI 75, PASI 100, sPGA clear and DLQI 0/1 at Week 16, while the key secondary endpoint for Part B was sPGA clear/almost clear at Week 104.

A total of 507 patients were randomised and included in the ITT and safety populations in Part A (risankizumab: 407; placebo: 100). 399 patients initially randomised to risankizumab continued to Part B (non-responders: 63; responders: 336). Among the responders, 225 patients were randomised to drug withdrawal (placebo) and 111 were randomised to continue risankizumab therapy. In Part A, all subjects had around 110 days of exposure and in Part B, the mean exposure was 311.7 days in subjects re-randomised to placebo and 468.6 days in those re-randomised to risankizumab.

Overall, the demographics and baseline characteristics were similar between the risankizumab and placebo groups in Parts A and B and all had moderate to severe disease as measured by PGA and PASI. The treatment groups were balanced with regard to prior medication history – 46% of all patients had previously received non-biologic systemic therapy and 36.5% had prior exposure to TNF antagonists.

In Part A, risankizumab was superior to placebo in terms of PASI 90 and sPGA clear/almost clear at Week 16. The adjusted difference in PASI 90 response was 70.8% (95%CI 65.7%, 76.0%; p<0.0001), while that in sPGA clear/almost clear was 76.5% (95%CI 70.4%, 82.5%; p<0.0001). The primary efficacy results for Part A were consistent in various sensitivity analyses based on different subgroups, demonstrating robustness of the data. Superiority over placebo was also shown in terms of key secondary endpoints. The results from the primary and secondary parameters in Part A were similar to those from ULTIMMA-1 and ULTIMMA-2.

In Part B, patients who continued risankizumab treatment were more likely to maintain an sPGA clear/almost clear response at Week 52 than those who were randomised to treatment withdrawal – the adjusted difference was 25.9% (95%CI 17.3%, 34.6%; p<0.001). At Week 104, 81.1% of subjects on sustained risankizumab achieved sPGA clear/almost clear. On the other hand, among those who were withdrawn from treatment, 61.3% achieved sPGA clear/almost clear at Week 52 compared to 7.1% at Week 104. 153 of 225 (68%) subjects who were re-randomised to placebo experienced relapses (sPGA≥3) and subsequently received at least one dose of re-treatment. After 16 weeks of re-treatment, 83.7% (128/153) regained sPGA of clear or almost clear, while 75.8% (116/153) achieved PASI 90. On the other hand, 4 of 111 subjects (3.6%) who were re-randomised to continue risankizumab went on to experience treatment relapses and received a loading dose at least 16 weeks prior to the re-

treatment data cut-off. Of these, 2 regained sPGA clear/almost clear at Week 16 of rescue treatment.

Summary of Key Efficacy Results (IMMhance)

Part A		
	PBO N = 100	**RZB N = 407**
Co-primary endpoints		
PASI 90 at Week 16		
n (%)	2 (2.0)	298 (73.2)
Adjusted Difference	70.8%	
95% CI	65.7, 76.0	
p-value	<0.001	
sPGA clear or almost clear at Week 16		
n (%)	7 (7.0)	340 (83.5)
Adjusted Difference	76.5%	
95% CI	70.4, 82.5	
p-value	<0.001	
Key Secondary Endpoint		
PASI 75 at Week 16		
n (%)	8 (8.0)	361 (88.7)
Adjusted Difference	80.6%	
p-value	<0.001	
PASI 100 at Week 16		
n (%)	1 (1.0)	192 (47.2)
Adjusted Difference	45.5%	
p-value	<0.001	
sPGA clear at Week 16		
n (%)	1 (1.0)	189 (46.4)
Adjusted Difference	44.8%	
p-value	<0.001	
DLQI 0/1 at Week 16		
n (%)	3 (3.0)	266 (65.4)
Adjusted Difference	62.1%	
p-value	<0.001	
Part B (re-randomised patients only)		
	RZB/RZB/PBO N = 225	**RZB/RZB/RZB N = 111**
Primary endpoints		
sPGA clear or almost clear at Week 52		
n (%)	138 (61.3)	97 (87.4)
Adjusted Difference	25.9%	
95% CI	17.3, 34.6	
p-value	<0.001	
Key Secondary Endpoint		
sPGA clear or almost clear at Week 104		
n (%)	16 (7.1)	90 (81.1)
Adjusted Difference	73.9%	
95% CI	66.0, 81.9	
p-value	<0.001	

PBO: placebo; RZB: risankizumab

There were 63 non-responders entering Part B of the study went on to continue risankizumab as open-label treatment. Of these, 38.1% and 50.8% achieved sPGA clear or almost clear at Weeks 32 and 52, respectively, compared to 6.3% at Week 28, showing that some subjects

require a longer period of sustained treatment after the first 16 weeks before clinically relevant improvements are achieved.

Overall, the results of the four studies were consistent in meeting the primary and secondary efficacy endpoints, and adequately supported the efficacy of risankizumab for the preventive treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of risankizumab through 16 weeks was based primarily on safety data from the Phase 2 and Phase 3 studies in patients with plaque psoriasis, where risankizumab data was compared to data from 300 patients receiving placebo, 239 subjects receiving ustekinumab and 304 subjects receiving adalimumab. From the plaque psoriasis studies unblinded at the time of submission, a total of 2234 patients received at least one dose of risankizumab, with 1590 subjects having received 150 mg from randomisation or after switching from placebo. The median exposure of the 150 mg group was 401.0 days compared to 369.0 days in the all-risankizumab group.

The safety analysis of risankizumab mainly comprised three integrated data sets reflecting the short- and long-term safety in the target patient population. The Primary Safety Pool included patients with psoriasis randomised to multiple dose treatment through Week 16 in the four pivotal studies and the Phase 2 dose-ranging study. The Ustekinumab-Controlled Analysis Set included patients with psoriasis randomised to risankizumab 150 mg or ustekinumab up to Week 52. The All Risankizumab Psoriasis Analysis Set included patients with psoriasis who received a dose of risankizumab up to the end of exposure in the pivotal studies.

Overview of safety profile (Primary Safety Pool, 16 weeks)

AE n (%)	Placebo (N=300)	Ustekinumab (N=239)	Adalimumab (N=304)	Risankizumab 150 mg (N=1306)	Total Risankizumab (N=1389)
Any TEAE	145 (48.3)	125 (52.3)	173 (56.9)	638 (48.9)	681 (49.0)
Treatment-related TEAE	30 (10.0)	36 (15.1)	61 (20.1)	153 (11.7)	166 (12.0)
SAE	12 (4.0)	12 (5.0)	9 (3.0)	31 (2.4)	31 (2.2)
Treatment-related SAE	1 (0.3)	4 (1.7)	4 (1.3)	5 (0.4)	5 (0.4)
Discontinuations due to AE	9 (3.0)	3 (1.3)	6 (2.0)	9 (0.7)	10 (0.7)
Deaths due to AE	0	0	2 (0.7)	1 (<0.1)	1 (<0.1)

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Overview of safety profile (Ustekinumab-Controlled Analysis Set, 52 weeks)

AE n (%)	Ustekinumab (N=239)	Risankizumab 150 mg (N=1306)
Any TEAE	157 (78.9)	419 (70.1)
Treatment-related AE	52 (26.1)	119 (19.9)
SAE	18 (9.0)	42 (7.0)
Treatment-related SAE	5 (2.5)	5 (0.8)
Discontinuations due to AE	4 (2.0)	5 (0.8)
Deaths due to AE	0	1 (0.2)

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Overview of safety profile (All Risankizumab - Psoriasis Analysis Set)

AE n (%)	Risankizumab 150 mg (N=1590)	All Risankizumab (N=2234)
Any TEAE	1190 (74.8)	1480 (66.2)
Treatment-related AE	324 (20.4)	396 (17.7)
SAE	109 (6.9)	139 (6.2)
Treatment-related SAE	16 (1.0)	23 (1.0)
Discontinuations due to AE	29 (1.8)	35 (1.6)
Deaths due to AE	4 (0.3)	4 (0.2)

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

The most frequently reported treatment-emergent adverse events in all three analysis sets were upper respiratory tract infections, viral upper respiratory tract infections, headache and arthralgia. Most AEs were assessed by the investigators as having no reasonable possibility of being related to study drug across all treatment groups. The majority of AEs observed with risankizumab treatment were mild to moderate in severity, and this was consistently observed across the treatment groups. After 52 weeks, the incidence of TEAEs remained lower in the Risankizumab 150 mg group than in the ustekinumab group (70.1% vs 78.9%).

Treatment-related TEAEs that occurred with higher incidence in the risankizumab 150 mg arm compared to placebo in the Primary Safety Pool were upper respiratory tract infection (URTI) (1.2% vs 0.3%), viral URTI (0.9% vs 0.7%) and fatigue (1.0% vs 0.3%), whereas those which occurred with higher incidence in the risankizumab 150 mg arm compared to active comparators were fatigue (1.0% vs 0.8% (ustekinumab) and 0.7% (adalimumab)). In the longer term (up to 77 weeks), the safety profile of risankizumab was consistent with the profile observed up to 16 weeks.

SAE incidence was lower in the risankizumab group after 16 weeks of treatment (2.4%) compared to placebo (4.0%) and active comparators (ustekinumab: 5.0%; adalimumab: 3.0%). At Week 52, the exposure-adjusted SAE rate for risankizumab 150 mg was similar to that at Week 16 at 9.4E/100PY, compared to 10.4E/100PY for ustekinumab. The most frequently reported SAEs in risankizumab treated subjects were infection-related events, cardiac events and neoplasms. Overall 1% of the risankizumab population had treatment related SAEs. These were mainly bacterial infections, including pneumonia, sepsis, osteomyelitis and cellulitis but the exposure-adjusted rates of these AEs were generally comparable to background rates reported in published studies.

The incidence of AEs leading to study discontinuation was low in all groups in the Primary Safety Pool (≤3.0%). SAEs in risankizumab-treated subjects which led to study discontinuation in the Primary Safety Pool included one case each of cardiac failure congestive, drug-induced liver injury, liver injury, invasive lobular breast carcinoma, and oesophageal carcinoma. However, the numbers were too small for a clear safety signal to be identified.

The AEs of special interest reported with risankizumab included infections, malignancies, non-melanoma skin cancer (NMSC) and immunogenicity. The AEs of special interest from the Primary Safety Pool which occurred more frequently in the risankizumab group than in the placebo group were serious infections (0.4% vs 0.3%) and malignant tumours (excluding NMSC) (0.2% vs 0%). However, the incidence rates of these AEs were low and remained similar to background rates, hence a safety signal could not be confirmed. Nevertheless, infections, immunogenicity and hypersensitivity were described as warnings and precautions in the approved package insert.

Overall, risankizumab presented an acceptable safety profile for the target patient population which appeared similar to that of other IL-23 inhibitors. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Psoriasis is a chronic, immune-mediated inflammatory skin disease which has been estimated to affect 1-2% of the Singapore population and is among the most commonly treated skin diseases. While not generally life-threatening, psoriatic lesions can cause pain and pruritis, as well as profound psychological effects which negatively impact a patient's quality of life. Plaque psoriasis is the most common form of psoriasis and affects 80-90% of patients. Moderate to severe plaque psoriasis may be treated with topical therapy, phototherapy, conventional systemic chemical drugs, biologics and a combination of these agents.

The efficacy of risankizumab was consistently demonstrated in 4 pivotal studies, where a statistically significant responses against placebo and both active comparators (ustekinumab and adalimumab) after 16 weeks of treatment in terms of PASI 90 and sPGA clear/almost clear response. These results were also supported by the secondary endpoints at either earlier (Week 12) or later (Week 52) time points. Risankizumab also resulted in meaningful improvement in psoriasis symptoms (itch, pain, burning and redness), with nearly a third of subjects reporting no symptoms by Week 16 of treatment and about 56% reporting no symptoms by Week 52.

Risankizumab also produced clinically meaningful and statistically significant improvements in the quality of life after 16 weeks of treatment compared with placebo and adalimumab. Patients who received uninterrupted risankizumab treatment were more likely to maintain an sPGA clear/almost clear response at Week 52 than those who stopped treatment after achieving positive response – the adjusted difference was 25.9% (95%CI 17.3%, 34.6%; $p<0.001$). Maintenance of effect from continuous treatment over 52 weeks was demonstrated in ULTIMMA-1 and ULTIMMA-2 and over 104 weeks in IMMhance compared to placebo, and over 44 weeks when compared to adalimumab.

The safety profile of risankizumab was considered acceptable and similar to other IL-23 inhibitors. Adverse events generally occurred at a similar incidence in the risankizumab-treated subjects compared to those who received placebo or active comparators. The most notable safety concerns were hypersensitivity, infections and immunogenicity, which have been adequately addressed in the package insert.

Overall, the benefit-risk profile of risankizumab for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Skyrizi for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy and phototherapy was deemed favourable and approval of the product registration was granted on 06 July 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

SKYRIZI™ SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 75MG/0.83mL (risankizumab)

1. PRODUCT NAME

1.1 Generic name

risankizumab

1.2 Trade name

SKYRIZI™

2. INDICATIONS

SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

3. DOSAGE AND ADMINISTRATION

3.1 Recommended dosage

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

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

3.2 Missed dose

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

3.3 Dosing in special populations

3.3.1 Pediatrics

The safety and efficacy of SKYRIZI in pediatric patients less than 18 years of age have not yet been established.

3.3.2 Geriatric

No dose adjustment is required *(see* **PHARMACOLOGIC PROPERTIES***)*.

There is limited information in subjects aged ≥ 65 years.

3.3.3 Renal or hepatic impairment

No specific studies were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of SKYRIZI. 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* **PHARMACOLOGIC PROPERTIES***)*.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 15.2

Clinically important active infections (e.g. active tuberculosis, see section 5.1)

5. WARNINGS AND PRECAUTIONS

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

5.1 Infections

SKYRIZI may increase the risk of infections.

In patients with a chronic infection, a history of recurrent infection or known risk factors for infection, the risks and benefits should be considered prior to prescribing SKYRIZI. Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Patients should be instructed to seek medical advice if signs or symptoms of clinically important 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 SKYRIZI should not be administered until the infection resolves.

Tuberculosis

Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent tuberculosis (TB) who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on risankizumab.

Prior to initiating treatment with SKYRIZI, patients should be evaluated for TB infection. SKYRIZI must not be given to patients with active TB. Patients receiving SKYRIZI should be monitored for signs and symptoms of active TB. In patients with latent TB, consider anti-TB therapy prior to initiating SKYRIZI.

5.2 Immunizations

Prior to initiating therapy with SKYRIZI, completion of all appropriate immunizations should be considered according to current immunization guidelines. SKYRIZI should not be used with live vaccines. No data are available on the response to live or inactive vaccines.

5.3 Hypersensitivity

If a serious hypersensitivity reaction occurs, administration of SKYRIZI should be discontinued immediately and appropriate therapy initiated.

6. DRUG INTERACTIONS

SKYRIZI is not expected to undergo metabolism by hepatic enzymes or renal elimination. Drug interactions between SKYRIZI and inhibitors/inducers of drug metabolizing enzymes are not expected.

Based on results from a drug-drug interaction study in subjects with plaque psoriasis and population pharmacokinetic analyses, risankizumab would not cause or be impacted by drug-drug interactions *(see* **PHARMACOLOGIC PROPERTIES***)*.

No dose adjustment is needed when co-administering risankizumab and cytochrome P450 substrates.

7. PREGNANCY AND LACTATION

7.1 Pregnancy

The limited data available with SKYRIZI use in pregnant women are insufficient to inform any drug-associated risks. As a precautionary measure, it is preferable to avoid the use of SKYRIZI during pregnancy.

7.1.1 Data (animal and/or human)

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab at 5 and 50 mg/kg from gestation day 20 to parturition and the cynomolgus monkeys (mother and infants) were followed for 6 months (180 days) after delivery. These doses produced exposures of up to approximately 70 times the clinical exposure at the maximum recommended human dose (MRHD). No drug-related fetal/infant deaths and/or malformations were observed. There were no effects on infant growth and development, which included the assessment of external, visceral, skeletal and neurobehavioral parameters and developmental immunotoxicology endpoints. In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 20-90% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-treated groups had measurable serum concentrations of risankizumab up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

7.1.2 Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment.

7.2 Lactation

There are no data on the presence of risankizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Although human IgG is secreted into human milk, published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. A decision should be made whether to discontinue breast-

feeding or to discontinue SKYRIZI taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

8. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

9. ADVERSE REACTIONS

9.1 Clinical trials experience

A total of 2234 subjects were treated with SKYRIZI in clinical development studies in plaque psoriasis, representing 2167 subject-years of exposure. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled studies were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group. Serious adverse events occurred in 2.4% for the SKYRIZI group (9.9 events per 100 subject-years) compared to 4.0% for the placebo group (17.4 events per 100 subject-years), 5.0% for the ustekinumab group (18.4 events per 100 subject-years) and 3.0% for the adalimumab group (14.7 events per 100 subject-years).

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical studies.

Table 1. Adverse Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

Adverse Reactions	SKYRIZI[1,2,4] N = 1306 n (%)	Placebo[1,2] N = 300 n (%)	Ustekinumab[1,3] N = 239 n (%)	Adalimumab[4] N = 304 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)	28 (11.7)	42 (13.8)
Headache[b]	46 (3.5)	6 (2.0)	9 (3.8)	20 (6.6)
Fatigue[c]	33 (2.5)	3 (1.0)	7 (2.9)	8 (2.6)
Injection site reactions[d]	19 (1.5)	3 (1.0)	9 (3.8)	17 (5.6)
Tinea infections[e]	15 (1.1)	1 (0.3)	1 (0.4)	2 (0.7)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis
[1] Includes data from ULTIMMA-1 and ULTIMMA-2 studies

[2] Includes data from IMMHANCE study
[3] Includes data from Phase 2 Study 1311.2
[4] Includes data from IMMVENT study

Adverse reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 was folliculitis.

Specific Adverse Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared to 14.7% of the placebo group (56.5 events per 100 subject-years), 20.9% of the ustekinumab group (87.0 events per 100 subject-years) and 24.3% of the adalimumab group (104.2 events per 100 subject-years). The majority of cases were non-serious and mild to moderate in severity and did not lead to discontinuation of SKYRIZI.

Over the entire psoriasis program including long-term exposure to SKYRIZI, the rate of infections (75.5 events per 100 subject-years) was similar to that observed during the first 16 weeks of treatment.

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 SKYRIZI and 10.9 for those treated with ustekinumab. The safety profile of SKYRIZI with up to 77 weeks of exposure was consistent with the profile observed up to 16 weeks.

9.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with SKYRIZI. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity (including neutralizing antibody) in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to risankizumab with the incidence of antibodies to other products may be misleading.

For subjects treated with SKYRIZI at the recommended clinical dose for up to 52 weeks in psoriasis clinical trials, treatment-emergent anti-drug antibodies and neutralizing antibodies were detected in 24% (263/1079) and 14% (150/1079) of evaluated subjects, respectively.

For most subjects, antibodies to risankizumab including neutralizing antibodies were not associated with changes in clinical response or safety. Higher antibody titers observed in approximately 1% (7/1000 at Week 16 and 6/598 at Week 52) of subjects treated with SKYRIZI appeared to be associated with a reduced clinical response.

10. DRUG ABUSE AND DEPENDENCY

None.

11. 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.

12. PHARMACOLOGIC PROPERTIES

12.1 Mechanism of action

Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor complex. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. IL-23 supports the development, maintenance and activation of Th17 cells, which produces IL-17A, IL-17F, and IL-22, as well as other pro-inflammatory cytokines, and plays a key role in driving inflammatory autoimmune diseases, such as psoriasis. IL-23 is up-regulated in lesional skin in comparison to non-lesional skin of patients with plaque psoriasis. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signaling and release of proinflammatory cytokines.

Risankizumab does not bind to human IL-12, which shares the p40 subunit with IL-23.

12.2 Pharmacodynamics

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.

12.3 Pharmacokinetics

12.3.1 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 1200 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 the dosing regimen in subjects with psoriasis (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.

12.3.2 Distribution

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.

12.3.3 Metabolism

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 metabolized by cytochrome P450 enzymes.

12.3.4 Excretion

The systemic clearance (CL) of risankizumab was 0.31 L/day and terminal elimination half-life was 28 days for a typical 90 kg subject 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.

12.3.5 Drug interactions

A drug 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 (CYP3A4 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 medications (metformin, atorvastatin, lisinopril, amlodipine, ibuprofen, acetylsalicylate and levothyroxine) used by some subjects with plaque psoriasis during the clinical studies *(see* **DRUG INTERACTIONS***)*.

12.4 Pharmacokinetics in special populations

12.4.1 Pediatric

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

12.4.2 Geriatric

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 were 65 years or older and 24 subjects were 75 years or older. No overall differences in risankizumab exposure, safety and effectiveness were observed between older and younger subjects who received SKYRIZI *(see* **DOSAGE AND ADMINISTRATION***)*.

12.4.3 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.

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 *(see* **DOSAGE AND ADMINISTRATION***)*.

12.4.4 Body weight

Risankizumab clearance and volume of distribution increase as body weight increases. However, clinically meaningful changes in efficacy and safety of risankizumab were not observed with increased body weight, therefore no dose adjustment is necessary based on body weight.

12.4.5 Gender or race

The clearance of risankizumab was not significantly influenced by gender or race in adult subjects with plaque psoriasis. No clinically meaningful differences in risankizumab exposure were observed in Chinese or Japanese subjects compared to Caucasian subjects in a clinical pharmacokinetic study.

13. CLINICAL STUDIES

The efficacy and safety of SKYRIZI was assessed in 2109 subjects with moderate to severe plaque psoriasis in four multicenter, randomized, 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, and a Psoriasis Area and Severity Index (PASI) score ≥12.

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

Across all studies, 38.1% of subjects had received prior phototherapy, 48.3% had received prior non-biologic systemic therapy, and 42.1% had received prior biologic therapy for the treatment of psoriasis. Of the subjects who had received prior biologic therapy, 23.7% had received at least one anti-TNF alpha agent.

ULTIMMA-1 and ULTIMMA-2

ULTIMMA-1 and ULTIMMA-2 enrolled 997 subjects (598 randomized to SKYRIZI 150 mg, 199 to ustekinumab 45 mg or 90 mg, and 200 to placebo). Subjects received treatment at Week 0, Week 4, and every 12 weeks thereafter. The results are presented in Table 2 and Figure 1.

Table 2. Efficacy Results in Adults with Plaque Psoriasis in ULTIMMA-1 and ULTIMMA-2

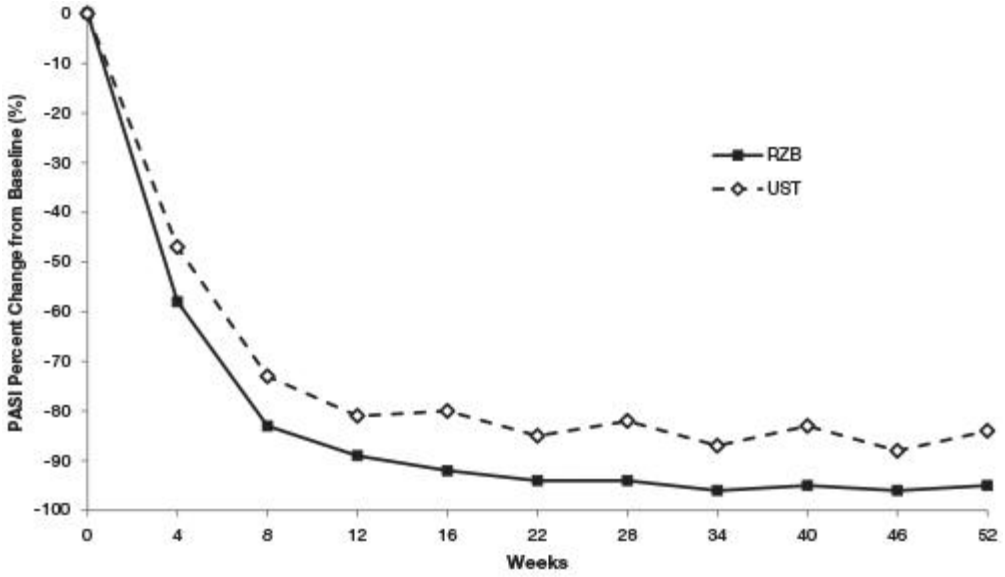
	ULTIMMA-1	**ULTIMMA-2**

	SKYRIZI (N=304) n (%)	Ustekinumab (N=100) n (%)	Placebo (N=102) n (%)	SKYRIZI (N=294) n (%)	Ustekinumab (N=99) n (%)	Placebo (N=98) n (%)
sPGA of clear or almost clear (0 or 1)						
Week 12	250 (82.2)	65 (65.0)	9 (8.8)	242 (82.3)	64 (64.6)	9 (9.2)
Week 16	267 (87.8)[a]	63 (63.0)	8 (7.8)	246 (83.7)[a]	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	229 (75.3)[a]	42 (42.0)	5 (4.9)	220 (74.8)[a]	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)	—

All comparisons of SKYRIZI 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

Figure 1. Time Course of Mean Percent Change from Baseline of PASI in ULTIMMA-1 and ULTIMMA-2



RZB = risankizumab

UST = ustekinumab
p<0.001 at each time point

Examination of age, gender, race, body weight, 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 SKYRIZI 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 SKYRIZI.

IMMHANCE

IMMHANCE enrolled 507 subjects (407 randomized to SKYRIZI 150 mg and 100 to placebo). Subjects received treatment at Week 0, Week 4 and every 12 weeks thereafter. Subjects who were originally on SKYRIZI and had an sPGA response of clear or almost clear at Week 28 were re-randomized to continue SKYRIZI every 12 weeks or have treatment withdrawn.

At Week 16, SKYRIZI was superior to placebo on the co-primary endpoints of sPGA of clear or almost clear (83.5% SKYRIZI vs 7.0% placebo) and PASI 90 (73.2% SKYRIZI vs 2.0% placebo). More subjects on SKYRIZI had clear skin [sPGA 0 (46.4% SKYRIZI vs 1.0% placebo) or PASI 100 (47.2% SKYRIZI vs 1.0% placebo)] at Week 16. Subjects receiving SKYRIZI were also more likely to have a PASI 75 response compared with placebo (88.7% SKYRIZI vs 8.0% 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 SKYRIZI maintained this response at week 104 compared to 7.1% (16/225) who were re-randomised to withdrawal from SKYRIZI. Of these subjects, 63.1% (70/111) of subjects re-randomised to continued treatment with SKYRIZI achieved a sPGA clear response at week 104 compared to 2.2% (5/225) who were re-randomised to withdrawal from SKYRIZI.

IMMVENT

IMMVENT enrolled 605 subjects (301 randomized to SKYRIZI and 304 to adalimumab). Subjects randomized to SKYRIZI received 150 mg of treatment at Week 0, Week 4 and every 12 weeks thereafter. Subjects randomized 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 SKYRIZI
- PASI 50 to <PASI 90 were re-randomized to either continue adalimumab or switch to SKYRIZI
- PASI 90 continued to receive adalimumab

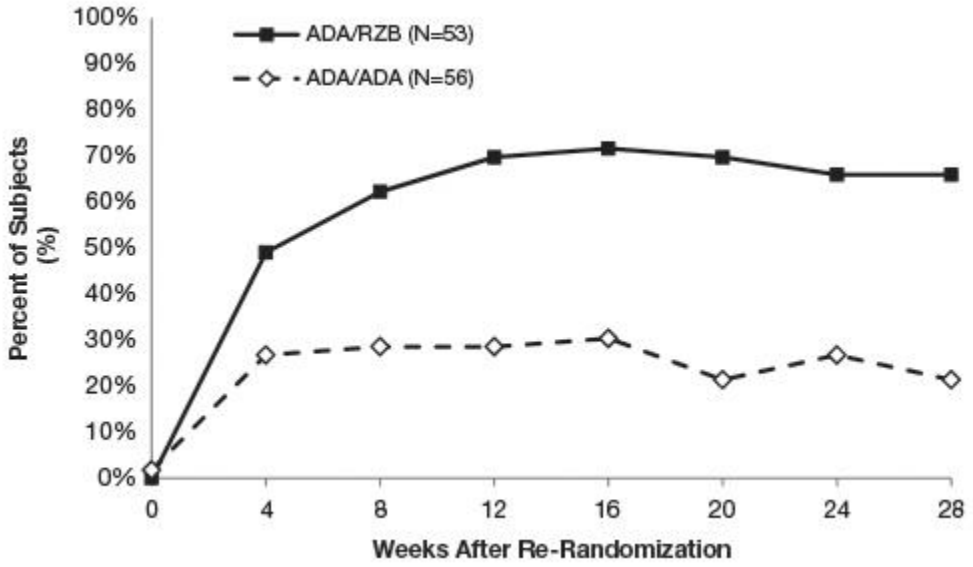
Similar results for SKYRIZI at Week 16 were seen in IMMVENT as in other clinical studies (Table 3 and Figure 2).

Table 3. Efficacy Results at Week 16 in Adults with Plaque Psoriasis in IMMVENT

	SKYRIZI (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)
All comparisons achieved p<0.001 [a] Co-primary endpoints		

For subjects who had PASI 50 to <PASI 90 with adalimumab at Week 16 and were re-randomized, differences in PASI 90 response rates between switching to SKYRIZI and continuing adalimumab were noted as early as 4 weeks after re-randomization (49.1% vs 26.8%, respectively). 66.0% (35/53) of subjects achieved PASI 90 following 28 weeks of SKYRIZI, compared with 21.4% (12/56) who continued to receive adalimumab. Other levels of response were also higher following SKYRIZI: 39.6% PASI 100, 39.6% sPGA clear, and 73.6% sPGA clear or almost clear had response after switching to SKYRIZI, compared with 7.1% PASI 100, 7.1% sPGA clear, and 33.9% sPGA clear or almost clear who continued to receive adalimumab.

Figure 2. Time Course of PASI 90 After Re-randomization in IMMVENT



ADA/ADA: Subjects randomized to adalimumab and continued on adalimumab
ADA/RZB: Subjects randomized to adalimumab and switched to SKYRIZI
p<0.05 at Week 4 and p<0.001 at each time point beginning at Week 8

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

Maintenance and Durability of Response

In an integrated analysis of subjects receiving SKYRIZI in ULTIMMA-1 and ULTIMMA-2 for PASI 100 responders at Week 16, 79.8% (206/258) of the subjects who continued on SKYRIZI 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.

Among subjects with sPGA of clear or almost clear at Week 28 in IMMHANCE, 87.4% (97/111) of subjects re-randomized to continued treatment with SKYRIZI maintained this response at Week 52 compared to 61.3% (138/225) who were re-randomized to withdrawal from SKYRIZI.

Quality of Life/Patient-Reported Outcomes

Significantly more subjects treated with SKYRIZI achieved a Dermatology Life Quality Index (DLQI) score of 0 or 1 [no impact on health-related quality of life] at Week 16 compared with placebo, adalimumab, or ustekinumab (Table 4). Improvement in health-related quality of life continued through Week 52 (ULTIMMA-1 and ULTIMMA-2).

Table 4. Health-related Quality of Life in ULTIMMA-1, ULTIMMA-2, and IMMVENT

	ULTIMMA-1			**ULTIMMA-2**			**IMMVENT**	
	SKYRIZI (N=304) n (%)	**Ustekinumab (N=100) n (%)**	**Placebo (N=102) n (%)**	**SKYRIZI (N=294) n (%)**	**Ustekinumab (N=99) n (%)**	**Placebo (N=98) n (%)**	**SKYRIZI (N=301) n (%)**	**Adalimumab (N=304) n (%)**
DLQI 0 or 1								
Week 16	200 (65.8)	43 (43.0)	8 (7.8)	196 (66.7)	46 (46.5)	4 (4.1)	198 (65.8)	148 (48.7)
Week 52	229 (75.3)	47 (47.0)	--	208 (70.7)	44 (44.4)	--	--	--
All comparisons of SKYRIZI versus ustekinumab, adalimumab and placebo achieved p<0.001								

In ULTIMMA-1 and ULTIMMA-2, significantly greater improvements in psoriasis symptoms (itch, pain, redness and burning, as measured by the Psoriasis Symptom Score [PSS]) were demonstrated with SKYRIZI compared to placebo at Week 16. A significantly greater proportion of subjects on SKYRIZI achieved a PSS of 0 (symptom-free) at Week 16 compared with ustekinumab and with placebo. By Week 52, 55.7% (333/598) of subjects on SKYRIZI reported no itch, pain, redness or burning.

Anxiety and depression, as measured by the Hospital Anxiety and Depression Scale (HADS) improved in the SKYRIZI group at Week 16 compared with those receiving placebo in ULTIMMA-1 and ULTIMMA-2.

A greater improvement in the Work Limitations Questionnaire (WLQ) at Week 16 was achieved in subjects receiving SKYRIZI compared with those receiving adalimumab in IMMVENT.

14. PRE-CLINICAL SAFETY DATA

Non-clinical data revealed no special hazard for humans based on repeat-dose toxicity studies including safety pharmacology evaluations, and a reproductive and 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]).

14.1 Carcinogenicity

Carcinogenicity studies have not been conducted with SKYRIZI. 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.

14.2 Mutagenicity

Mutagenicity studies have not been conducted with SKYRIZI.

14.3 Impairment of fertility

Studies in cynomolgus monkeys at doses of up to 50 mg/kg/week (about 70 times the clinical exposure at the MRHD) with SKYRIZI did not indicate direct or indirect harmful effects on male or female fertility. In the 26-week repeat dose toxicology study, histopathology of reproductive organs from both male and female cynomolgus monkeys did not show any relevant adverse finding. In a 26-week repeat dose study in sexually mature male cynomolgus monkeys, no effects on male fertility parameters were observed.

14.4 Animal pharmacology and/or toxicology

In a 26-week toxicology study with weekly subcutaneous doses of up 50 mg/kg, no adverse effects were observed in male and female cynomolgus monkeys at exposures of about 70 times higher than the clinical exposure at the MRHD.

15. PHARMACEUTICAL PROPERTIES

15.1 Description

Risankizumab, an interleukin-23 blocker, is a humanized immunoglobin G1 (IgG1) monoclonal antibody. Risankizumab is produced in a mammalian cell line using recombinant DNA technology.

The solution is colorless to slightly yellow and clear to slightly opalescent. It may contain a few translucent to white product-related particles. SKYRIZI should not be used if the solution is cloudy or discolored, or contains large particles. Each prefilled syringe contains 75 mg risankizumab in 0.83 mL solution.

15.2 List of excipients

Each prefilled syringe contains disodium succinate hexahydrate , succinic acid , sorbitol , polysorbate 20 and water for injection.

15.3 Information about certain excipients

This medicinal product contains 68.0 mg sorbitol per 150 mg dose.

This medicinal product contains less than 1 mmol sodium (23 mg) per 150 mg dose, i.e. essentially ‘sodium-free’.

15.4 Important instructions

Patients may self-inject SKYRIZI after training in subcutaneous injection technique.

Patients should be instructed to inject 2 prefilled syringes for the full 150 mg dose and to read the Instructions for Use before administration. Each prefilled syringe is for single use only.

For each dose, the injections should be administered at different anatomic locations (such as thighs or abdomen), and not 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.

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 prefilled syringes from the carton.

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

15.5 Storage

Store in a refrigerator at 2° C to 8° C. Do not freeze. Keep the prefilled syringes in the outer carton in order to protect from light.

15.6 How supplied

SKYRIZI is supplied as a solution for injection in prefilled syringe with needle guard.

Each carton contains 2 prefilled syringes and 2 alcohol pads

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Date of issue: 06 Jul 2020