CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

RISANKIZUMAB (SKYRIZI)

(AbbVie)

Indication: For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

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Abbreviations

AE	adverse event
BSA	body surface area
CDR	CADTH Common Drug Review
CI	confidence interval
DLQI	Dermatology Life Quality Index
HRQoL	health-related quality of life
ICER	Institute for Clinical and Economic Review
IL	interleukin
ITC	indirect treatment comparison
ITT	intention-to-treat population
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
MCID	minimal clinically important difference
NAb	neutralizing antibodies
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NRI	nonresponder imputation
OLE	open-label extension
PASI	Psoriasis Area and Severity Index
PP	per-protocol
PSI	Psoriasis Symptom Inventory
PSS	Psoriasis Symptoms Scale
SAE	serious adverse event
SC	subcutaneous
sPGA	static Physician Global Assessment
TNF	tumour necrosis factor

Drug	Risankizumab (Skyrizi)
Indication	For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Reimbursement Request	• Reimburse in a manner similar to other biologics for the treatment of moderate to severe plaque psoriasis. • Treatment should be discontinued if a response (PASI 75) to treatment with risankizumab has not been demonstrated after 16 weeks.
Dosage Form(s)	Solution for injection in a pre-filled syringe; 90 mg/mL (75 mg risankizumab in 0.83 mL solution)
NOC Date	April 17, 2019
Manufacturer	AbbVie

Executive Summary

Introduction

Plaque psoriasis is a chronic, inflammatory skin disease caused in part by dysregulation of the immune system. Psoriasis is driven primarily by pathogenic T-cells that produce high levels of interleukin 17 (IL-17) and tumour necrosis factor (TNF) alpha in response to interleukin 23 (IL-23).[1] Psoriasis is characterized by the presence of erythematous inflammatory plaques that may be itchy or painful and are usually covered by silver, flaking scales.[1,2] It is estimated that approximately one million Canadians are living with psoriasis.[3] Plaque psoriasis is the most common form and represents approximately 90% of cases.[3] Approximately 35% of patients with psoriasis have moderate to severe disease.[4]

Standard treatment for moderate to severe plaque psoriasis often involves systemic therapies, such as cyclosporine and methotrexate, but long-term use of these drugs is limited by toxicity. While effective for rapid disease control, biologic drugs such as TNF-alpha inhibitors (adalimumab, etanercept, and infliximab) are associated with safety concerns including serious infections, autoimmune conditions, and malignancies.[5,6] Other biologic drugs more recently approved by Health Canada include the IL-23 inhibitor guselkumab, the IL-12/23 inhibitor ustekinumab, and IL-17 inhibitors secukinumab, ixekizumab, and brodalumab. However, their use is associated with serious infections, potential activation of inflammatory bowel disease in the case of IL-17 inhibitors, and suicidal ideation in the case of brodalumab.[7-17] According to the clinical expert consulted for this review, IL-17 and IL-23 inhibitors have replaced the TNF-alpha inhibitors as the most commonly used biologic treatments in Canada.

Risankizumab (Skyrizi) is another IL-23 inhibitor indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. It is available as a solution for injection in a single-use, pre-filled syringe containing 75 mg of risankizumab in 0.83 mL sterile solution (90 mg/mL). The recommended dose of risankizumab is 150 mg (two 75 mg injections) administered by subcutaneous (SC) injection at week 0, week 4, and every 12 weeks thereafter.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of risankizumab for the treatment of moderate to severe plaque psoriasis in adults.

Results and Interpretation

Included Studies

A total of four phase III randomized controlled trials (RCTs) met the pre-specified inclusion criteria identified in the review protocol, and were included in this CADTH Common Drug Review (CDR) systematic review: UltIMMA-1 (N = 506), UltIMMA-2 (N = 491), IMMhance (N = 507), and IMMvent (N = 605). All four trials had similar inclusion and exclusion criteria and enrolled patients with moderate to severe plaque psoriasis (defined as body surface area [BSA] involvement ≥ 10%, a Psoriasis Area and Severity Index [PASI] score of ≥ 12, and a static Physician Global Assessment [sPGA] score of ≥ 3, as per the inclusion criteria for each study). Each of the studies was conducted in two parts (A and B); treatment duration (16 weeks) and co-primary end points (PASI 90 [90% reduction from baseline PASI score]) and an sPGA score of 0 or 1 [clear or almost clear]) were identical in Part A of each study. In each study, patients were randomized to double-blind treatment in blocks and stratified by body weight (≤ 100 kg versus > 100 kg) and prior exposure to TNF antagonists. All studies included patients across multiple sites in Canada.

UltIMMA-1 and UltIMMA-2 were identically designed multi-centre, randomized, double-blind, double-dummy, placebo-controlled, active comparator–controlled studies. Part A (week 0 to 16) was a 16-week double-blind treatment period in which patients were randomized in a 3:1:1 ratio to treatment with either risankizumab (150 mg SC), ustekinumab (45 mg or 90 mg SC for patients ≤ 100 kg or > 100 kg, respectively) or placebo SC at weeks 0 and 4. In Part B (week 16 to 52), all patients randomized to placebo in Part A were switched to treatment with risankizumab (150 mg every 12 weeks), while patients randomized to risankizumab or ustekinumab continued their assigned treatment (risankizumab every 12 weeks or ustekinumab at weeks 16, 28, and 40) up to week 40 and were followed up to week 52.

IMMhance was a multi-centre, randomized, double-blind, placebo-controlled trial. In Part A1 (week 0 to 16) patients were randomized in a 4:1 ratio to either risankizumab 150 mg or placebo SC at weeks 0 and 4 up to week 16. At week 16 (Part A2) all patients originally randomized to placebo received treatment with risankizumab 150 mg SC every 12 weeks. Patients originally randomized to risankizumab continued their treatment every 12 weeks up to week 28 (beginning of Part B), at which time all patients were assessed for response to risankizumab based on their sPGA score. IMMhance is currently ongoing and interim results up to week 52 were available for this review. However, the results of Part B (maintenance of response following withdrawal of risankizumab and re-treatment in patients who relapse) are of limited relevance to the current review, as the treatment administration schedule does not reflect how risankizumab will be used in Canada, based on current clinical practice.

IMMvent was a multi-centre, randomized, double-blind, double-dummy, active-controlled trial designed to compare risankizumab with adalimumab (Part A, weeks 0 to 16), and followed by switching patients who had an inadequate response to adalimumab to risankizumab versus continuing treatment with adalimumab (Part B, week 16 to 44).

In Part A, patients were randomized in a 1:1 ratio to either risankizumab (150 mg at weeks 0 and 4) or adalimumab (80 mg at randomization, and 40 mg starting at week 1 and every other week thereafter) SC up to week 16. Those who were responders and nonresponders to adalimumab either continued adalimumab treatment or were switched to risankizumab,

respectively. Results of Part B from the IMMvent study support the efficacy of switching to risankizumab in patients who to adalimumab, which is likely one scenario in which risankizumab will be used in Canadian clinical practice.

Efficacy

The key efficacy outcomes identified in the review protocol were health-related quality of life (HRQoL), measures of skin clearance (PASI response and sPGA), and patient-reported symptoms. These outcomes were also identified as important to patients based on patient input submissions received for this CDR review.

In all four included trials, HRQoL was measured using the validated Dermatology Life Quality Index (DLQI) instrument. The score on the DLQI ranges from 0 to 30. A score of 0 to 1 means that patient HRQoL is not affected; the higher the score, the greater the impairment in HRQoL. Overall, treatment with risankizumab resulted in an improved HRQoL at 16 weeks after administering the induction regimen (two doses of risankizumab 150 mg SC at weeks 0 and 4) in each of the four trials. A statistically significantly larger proportion of patients achieved a DLQI score of 0 or 1 at week 16 in the risankizumab group compared with the ustekinumab group in UltIMMA-1 (65.8% versus 43.0%, adjusted difference: 23.0; 95% confidence interval [CI], 11.9 to 34.0; $P < 0.001$) and UltIMMA-2 (66.7% versus 46.5%, adjusted difference: 20.2; 95% CI, 9.1 to 31.4; $P < 0.001$). In IMMvent, more patients in the risankizumab group achieved a DLQI score of 0 at week 16 than in the adalimumab group (65.8% versus 48.7%, adjusted difference: [redacted]), but this outcome was not included as a ranked secondary end point. The patients on risankizumab appeared to continue to maintain improved HRQoL over ustekinumab up to week 52 in Part B of UltIMMA-1 and UltIMMA-2. Although DLQI score was not included in the statistical hierarchy in Part B of any trials included in this review, given the magnitude of the statistical significance of these results, it is unlikely that type I error affected these results.

Mean (standard error [SE]) change from baseline in DLQI at week 16 was statistically significantly greater in the risankizumab group compared with: the ustekinumab group in UltIMMA-1 ([redacted]) and UltIMMA-2 ([redacted]); and adalimumab (−11.5 [redacted] versus −9.7 [redacted], least squares ([LS] mean treatment difference [redacted]) in IMMvent. Change from baseline in DLQI was not a ranked secondary end point in any of the studies included in this review. Mean (SE) change from baseline in DLQI at week 52 was also statistically significantly greater in patients who continued risankizumab compared with those who continued ustekinumab ([redacted]) in UltIMMA-1 and UltIMMA-2 ([redacted]). In IMMvent, change from baseline DLQI score at week 44 was statistically significantly different between patients re-randomized to risankizumab versus adalimumab ([redacted]; LS mean difference: [redacted]). The recognized estimates of the minimal clinically important difference (MCID) for the DLQI range from 2.2 to 6.9.[18,19]

The magnitude of the treatment effect for PASI 90 and sPGA clear or almost clear at week 16 was approximately 20% in favour of risankizumab over ustekinumab or adalimumab in each study, which is clinically meaningful according to the clinical expert consulted for this CDR review. A statistically significantly larger proportion of patients

achieved PASI 90 at week 16 in the risankizumab group compared with: the ustekinumab groups in UltIMMA-1 (75.3% versus 42.0%, adjusted difference: 33.5; 95% CI, 22.7 to 44.3; $P < 0.001$) and UltIMMA-2 (74.8% versus 47.5%, adjusted difference: 27.6; 95% CI, 16.7 to 38.5; $P < 0.001$ for both), and the adalimumab group in IMMvent (72.4% versus 47.4%, adjusted difference: [redacted]; $P < 0.001$). Statistically significant results were also observed for the proportion of patients achieving PASI 100 at week 16 in each trial in favour of risankizumab. The proportion of patients who achieved PASI 90 at week 52 was statistically significantly greater in patients who continued treatment with risankizumab versus ustekinumab in both UltIMMA-1 (81.9% versus 44.0%, adjusted difference: 38.3; 95% CI, 27.9 to 48.6; $P < 0.001$) and UltIMMA-2 (80.6% versus 50.5%, adjusted difference: 30.2; 95% CI, 19.6 to 40.9; $P < 0.001$) trials. Similarly, a greater proportion of patients in the risankizumab group than in the ustekinumab group achieved PASI 100 at week 52 in both trials. In IMMvent, switching to risankizumab was superior to continuing adalimumab in the re-randomized patient population in terms of achieving PASI 90; 66.0% of patients re-randomized to risankizumab versus 21.4% of those who continued on adalimumab achieved PASI 90 at week 44 (adjusted difference: [redacted]; $P < 0.001$).

A statistically significantly larger proportion of patients achieved sPGA clear or almost clear at week 16 in the risankizumab group compared with: the ustekinumab groups in UltIMMA-1 (87.8% versus 63.0%, adjusted difference: 25.1; 95% CI, 15.2 to 35.0; $P < 0.001$) and UltIMMA-2 (83.7% versus 61.6%, adjusted difference: 22.3; 95% CI, 12.0 to 32.5; $P < 0.001$); and the adalimumab group in IMMvent (83.7% versus 60.2%, adjusted difference: [redacted]; $P < 0.001$). No MCID on the sPGA for patients with plaque psoriasis was identified. Similar results for sPGA clear or almost clear were observed at week 52 in each of the studies. In Part B of UltIMMA-1 and UltIMMA-2, the proportion of patients who achieved sPGA clear at week 52 was statistically significantly greater in patients who continued treatment with risankizumab compared with ustekinumab in UltIMMA-1 (57.6% versus 21.0%, adjusted difference: [redacted]; $P < 0.001$) and UltIMMA-2 (59.5% versus 30.3%, adjusted difference: [redacted]; $P < 0.001$). The proportion of patients who achieved sPGA clear or almost clear at week 52 was higher in the group that continued treatment with risankizumab compared with the group that continued with ustekinumab; however, this was not a ranked secondary end point and not controlled for multiplicity. At week 44 in IMMvent, in the re-randomized population, a higher proportion of patients re-randomized to risankizumab compared with those re-randomized to adalimumab achieved sPGA clear or almost clear ([redacted], respectively, adjusted difference: [redacted]) and sPGA clear ([redacted], respectively, adjusted difference: [redacted]) at week 44, but sPGA outcomes were not included in the ranked hierarchy for the statistical analysis and were not controlled for multiplicity.

All four trials included in this review took into account the potential impact of body weight and prior exposure to TNF antagonists on treatment response. Randomization was stratified based on body weight (≤ 100 kg versus > 100 kg) and prior TNF antagonist treatment (0 versus ≥ 1), and the stratified analysis was conducted on the co-primary end points. Results of this analysis were generally [redacted] to those observed in the full intention-to-treat (ITT) population in each of the four trials in that risankizumab was superior to ustekinumab or adalimumab for PASI 90 and sPGA clear or almost clear. [redacted]

[redacted]. Subgroup analyses on disease severity and history of psoriasis therapy (prior treatment with traditional systemic drugs or any other biologic treatment) were also conducted on the co-primary end points, with comparisons of risankizumab versus placebo conducted in UltIMMA-1, UltIMMA-2, and IMMhance, and versus adalimumab in IMMvent; no comparisons versus ustekinumab were conducted for these subgroup analyses. [redacted]. Overall, the results of the subgroup analyses do not identify any particular subgroup of patients whose condition would respond differently to treatment with risankizumab.

Patient-reported symptoms were measured by the Psoriasis Symptoms Scale (PSS). The proportion of patients who achieved a PSS score of 0 at week 16 in the risankizumab group versus the ustekinumab group was 29.3% versus 15.0% in UltIMMA-1 (adjusted difference: 14.3; 95% CI, 5.8 to 22.8; $P < 0.001$) and 31.3% versus 15.2% in UltIMMA-2 (adjusted difference: 16.1; 95% CI, 7.5 to 24.8; $P < 0.001$); the comparison between the risankizumab and ustekinumab groups was not included in the statistical analysis hierarchy in either study. The proportion of patients achieving a PSS score of 0 in Part B was also higher in patients treated with risankizumab compared with ustekinumab in UltIMMA-1 (56.9% versus 30.0%, adjusted difference: [redacted]; $P < 0.001$) and UltIMMA-2 (54.4% versus 30.3%, adjusted difference: [redacted]; $P < 0.001$), but this comparison was outside the statistical testing hierarchy for both studies and was not controlled for multiplicity. PSS was not measured in IMMhance or IMMvent in Part A or B of either study. Thus, whether risankizumab offers any benefit for patient-reported symptoms compared with adalimumab remains uncertain.

The results from Part B of UltIMMA-1 and UltIMMA-2 demonstrated that the response of risankizumab versus ustekinumab was maintained at week 52. That response was compared in patients on either risankizumab or ustekinumab throughout the duration of the study (i.e., randomized at the beginning of Part A).

The results of the two indirect treatment comparisons (ITCs) appraised in this CDR review suggest that over short-term (10 or 16 weeks) induction-treatment periods, the proportion of patients achieving PASI 75 or PASI 90 responses was significantly greater for risankizumab than for apremilast, etanercept, adalimumab, ustekinumab, infliximab, and secukinumab in patients with moderate to severe chronic plaque psoriasis; no significant difference for risankizumab versus ixekizumab, brodalumab or guselkumab was observed. [redacted] results were observed for PASI 100 in the ITC submitted by the manufacturer.

Harms

The proportion of patients experiencing an adverse event (AE) was similar or slightly lower in the risankizumab group versus the ustekinumab group in parts A and B of UltIMMA-1 and UltIMMA-2, and similar to placebo in both trials. In UltIMMA-1 and UltIMMA-2, the most frequently reported AEs across all parts of the studies were upper respiratory tract infection ([redacted] in UltIMMA-1; [redacted] in UltIMMA-2) and viral respiratory tract infection ([redacted] in UltIMMA-1; [redacted] in UltIMMA-2). These AEs were less common in the risankizumab group than in the ustekinumab group. In IMMhance, AEs occurred in a similar proportion of patients in the risankizumab (45.5%) and placebo

(48.0%) groups from week 0 to 16. A [redacted] proportion of patients in the re-randomized population experienced AEs during Part B (patients randomized to risankizumab in Part A and re-randomized to continue risankizumab [redacted] or switched to placebo [redacted] at week 28). In IMMhance, the most frequently reported AEs during Part B were [redacted] in patients who were re-randomized to continue on risankizumab and those who switched to placebo, respectively. In IMMvent, AEs occurred in a similar proportion of patients in the risankizumab (55.8%) and adalimumab (56.9%) groups. The most frequently reported AEs were [redacted]. In Part B, AEs were reported in a higher proportion of patients re-randomized to risankizumab (75.5%) than in patients re-randomized to adalimumab (66.1%).

Serious adverse events (SAEs) occurred infrequently regardless of the treatment period and treatment group in all four included trials. No SAE was observed in more than two patients in any study. The rate of withdrawal due to AEs was low (< 2.5%, with the exception of patients re-randomized to adalimumab in IMMvent [rate of 3.6%]) in all safety analysis populations across all studies, and was similar across treatment groups in both Part A and Part B of all studies included in this review. Treatment with risankizumab did not appear to be associated with increased mortality, as there were only seven deaths reported across the four included trials (i.e., two deaths each in UltIMMA-2 and IMMhance, and three deaths in IMMvent, with no deaths reported in UltIMMA-1).

Notable harms of interest to this review included infections, injection-site reactions, hypersensitivity events, immunogenicity, inflammatory bowel disease, major adverse cardiovascular events (MACE), and psychiatric symptoms. In the current review, the proportion of serious infection varied across trials and between treatment groups, but fungal infections were more common in patients treated with risankizumab (ranging from [redacted]). The proportion of patients experiencing injection-site reactions varied across trials and treatment groups but was less than 8% in any study.

In UltIMMA-1 and UltIMMA-2, a [redacted] proportion of patients in the risankizumab group ([redacted]) experienced hypersensitivity events during Part A than in the ustekinumab ([redacted]) groups, but hypersensitivity events occurred in a [redacted]). [redacted]). No anaphylactic reactions were reported in UltIMMA-1 or UltIMMA-2, IMMhance, or IMMvent.

The proportion of patients who experienced MACE ranged from no events in UltIMMA-1 to two events in each of UltIMMA-2, [redacted] and IMMvent. The incidence of inflammatory bowel disease was not reported in any of the studies, and no clear pattern of psychiatric symptoms emerged with risankizumab during UltIMMA-1, UltIMMA-2, IMMhance, or IMMvent.

Safety outcomes were reported in the ITC submitted by the manufacturer, which showed that [redacted]

[redacted].

Potential Place in Therapy[1]

The clinical expert consulted by CADTH noted there are nine biologics (including risankizumab) approved for the treatment of moderate to severe plaque psoriasis in Canada. Risankizumab is one of two anti–IL-23 drugs; the other one is guselkumab.

Biologics are currently used as continuous therapy. The clinical expert indicated that when a patient is started on a biologic, the treatment is expected to be continuous and lifelong. A major unmet need is a treatment that is remittive or would work well on an intermittent "as-needed" basis. So far, risankizumab and other biologics do not have clinical trial evidence in this regard and are not positioned in clinical practice to fulfill this need.

Risankizumab appears to be more efficacious than adalimumab and ustekinumab, based on the reviewed trials. The efficacy and safety profile of risankizumab seems similar to the other anti–IL-23 drug, guselkumab, but lacks head-to-head data. Risankizumab may be more convenient for patients, as it requires fewer injections (every 12 weeks versus every 8 weeks) compared with guselkumab. Risankizumab provides another choice for patients and physicians.

Conclusions

Overall, the four trials included in this review support risankizumab as an efficacious treatment with a safety profile at least similar to other biologics used for patients with moderate to severe plaque psoriasis. Three studies included active comparators to risankizumab: two were versus ustekinumab (UltIMMA-1 and UltIMMA-2) and one was versus adalimumab (IMMvent). Overall, after administration of the induction regimen, risankizumab demonstrated superior benefit to ustekinumab and adalimumab in terms of HRQoL and in PASI 90 and sPGA skin clearance scores at week 16. As shown in UltIMMA-1 and UltIMMA-2, the benefit of risankizumab over ustekinumab for PASI 90 and sPGA was maintained up to week 52. Further, in patients whose condition did not exhibit an adequate response to adalimumab, a higher proportion achieved PASI 90 after switching to risankizumab for 28 weeks compared with continuing adalimumab, as demonstrated in the IMMvent study. The included trials generally appear to have been performed with methodological rigour with low risk of bias and included a trial population that was reflective of patient characteristics and treatments typical of the Canadian context.

Other biologic treatments are associated with inflammatory bowel disease or psychiatric symptoms, and no such AEs were identified in the clinical trials of risankizumab included in this review. Treatment with risankizumab did not appear to be associated with an increased incidence of injection-site reactions or MACE [redacted].

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

There is no direct evidence comparing risankizumab with IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) or the IL-23 inhibitor guselkumab. Results of the two ITCs appraised in this CDR review suggest that over short-term induction-treatment periods (ranging from 10 to 16 weeks), the relative risk of achieving PASI 75 and PASI 90 responses is significantly greater for risankizumab than for placebo, apremilast, etanercept, adalimumab, ustekinumab, infliximab, and secukinumab in patients with moderate to severe chronic plaque psoriasis; no significant differences for risankizumab versus ixekizumab, brodalumab, or guselkumab were observed. [redacted]. There is uncertainty pertaining to the additional efficacy and safety benefit that long-term treatment with risankizumab may have over these newer biologic treatments.

Table 1: Summary of Key Results

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
PART A[a]										
Efficacy	**PBO (N = 102)**	**UST (N = 100)**	**RZB (N = 304)**	**PBO (N = 98)**	**UST (N = 99)**	**RZB (N = 294)**	**PBO (N = 100)**	**RZB (N = 407)**	**ADA (N = 304)**	**RZB (N = 301)**
Proportion of Patients Achieving a DLQI Score of 0 or 1 at Week 16 (NRI)										
n (%)	8 (7.8)	43 (43.0)	200 (65.8)	4 (4.1)	46 (46.5)	196 (66.7)	3 (3.0)	266 (65.4)	148 (48.7)	198 (65.8)
Adjusted difference vs. RZB (95% CI)	57.9 (50.4 to 65.3)[b]	23.0 (11.9 to 34.0)[b]	–	62.2 (55.5 to 68.9)[b]	20.2 (9.1 to 31.4)[b]	–	62.1 (56.4 to 67.9)[b]	–	17.1 (9.3 to 24.8)[b]	–
DLQI Change From Baseline to Week 16 (LOCF)										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	288	285
Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13.1	14.2
Week 16, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.4	1.8
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference, LS mean (SE) vs. RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	−2.5 to −1.1	–
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	< 0.001	–
Proportion of Patients Achieving PASI 90 at Week 16 (NRI)										
n (%)	5 (4.9)	42 (42.0)	229 (75.3)	2 (2.0)	47 (47.5)	220 (74.8)	2 (2.0)	298 (73.2)	144 (47.4)	218 (72.4)
Adjusted difference vs. RZB (95% CI)	70.3 (64.0 to 76.7)[b]	33.5 (22.7 to 44.3)[b]	–	72.5 (66.8 to 78.2)[b]	27.6 (16.7 to 38.5)[b]	–	[redacted]	[redacted]	24.9 (17.5 to 32.4)[b]	——
Proportion of Patients Achieving an sPGA Score of 0 or 1 (Clear or Almost Clear) at Week 16 (NRI)										
n (%)	8 (7.8)	63 (63.0)	267 (87.8)	5 (5.1)	61 (61.6)	246 (83.7)	7 (7.0)	340 (83.5)	183 (60.2)	252 (83.7)
Adjusted difference vs. RZB (95% CI)	79.9 (73.5 to 86.3)[b]	25.1 (15.2 to 35.0)[b]	–	78.5 (72.4 to 84.5)[b]	22.3 (12.0 to 32.5)[b]	–	[redacted]	[redacted]	[redacted]	–
Proportion of Patients Achieving a PSS of 0 at Week 16 (NRI)										
n (%)	2 (2.0)	15 (15.0)	89 (29.3)	0	15 (15.2)	92 (31.3)	NR	NR	NR	NR

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
Adjusted difference vs. RZB (95% CI)	27.1 (21.2 to 32.9)[b]	14.3 (5.8 to 22.8)[b]	–	31.2 (25.7 to 36.6)[b]	16.1 (7.5 to 24.8)[b]	–				
HARMS	**PBO (N = 102)**	**UST (N = 100)**	**RZB (N = 304)**	**PBO (N = 98)**	**UST (N = 99)**	**RZB (N = 294)**	**PBO (N = 100)**	**RZB (N = 407)**	**ADA (N = 304)**	**RZB (N = 301)**
AEs, N (%)	52 (51.0)	50 (50.0)	151 (49.7)	45 (45.9)	53 (53.5)	134 (45.6)	48 (48.0)	185 (45.5)	173 (56.9)	168 (55.8)
SAEs, N (%)	3 (2.9)	8 (8.0)	7 (2.3)	1 (1.0)	3 (3.0)	6 (2.0)	8 (8.0)	8 (2.0)	9 (3.0)	10 (3.3)
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 (2.3)	3 (1.0)
Deaths, N (%)	0	0	0	0	0	1 (0.3)	0	0	2 (0.7)	1 (0.3)
PART B										
EFFICACY	**PBO/RZB** (N = 97)	**UST/UST** (N = 100)	**RZB/ RZB** (N = 304)	**PBO/ RZB** (N = 9)	**UST/ UST** (N = 99)	**RZB/ RZB** (N = 294)	**RZB/ RZB/ PBO** (N = 225)[c]	**RZB/ RZB/RZB** (N = 111)[c]	**ADA/ ADA** (N = 56)[d]	**ADA/ RZB** (N = 53)[d]
Proportion of Patients Achieving a DLQI Score of 0 or 1										
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Adjusted difference vs. RZB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	
DLQI Change From Baseline (LOCF)										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
End of Part B, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Treatment difference, LS mean (SE) vs. RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Proportion of Patients Achieving PASI 90										
n (%)	76 (78.4)	44 (44.0)	249 (81.9)	80 (85.1)	50 (50.5)	237 (80.6)	[redacted]	[redacted]	12 (21.4)	35 (66.0)

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
Adjusted difference vs. RZB (95% CI)	–	38.3 (27.9 to 48.6)[b]	–	–	30.2 (19.6 to 40.9)[b]	–	[redacted]	[redacted]	45.0 [redacted]	
Proportion of Patients Achieving an sPGA Score of 0 or 1 (Clear or Almost Clear)										
n (%)	88 (90.7)	54 (54.0)	262 (86.2)	82 (87.2)	54 (54.5)	245 (83.3)	[redacted]	[redacted]	19 (33.9)	39 (73.6)
Adjusted difference vs. RZB (95% CI)	–	32.4 (22.0 to 42.9)[b]	–	–	29.1 (18.5 to 39.6)[b]	–	[redacted]		38.9 [redacted]	
HARMS	**PBO/RZB (N = 97)**	**UST/UST (N = 99)**	**RZB/ RZB (N = 297)**	**PBO/ RZB (N = 94)**	**UST/UST (N = 94)**	**RZB/RZB (N = 291)**	**RZB/ RZB/PBO (N = 225)**	**RZB/ RZB/RZB (N = 111)**	**ADA/ADA (N = 56)**	**ADA/RZB (N = 53)**
AEs, N (%)	65 (67.0)	66 (66.7)	182 (61.3)	61 (64.9)	70 (74.5)	162 (55.7)	[redacted]	[redacted]	37 (66.1)	40 (75.5)
SAEs, N (%)	3 (3.1)	4 (4.0)	16 (5.4)	3 (3.2)	4 (4.3)	13 (4.5)	[redacted]	[redacted]	2 (3.6)	3 (5.7)
WDAEs, N (%)	0	2 (2.0)	1 (0.3)	1 (1.1)	1 (1.0)	1 (0.3)	[redacted]	[redacted]	2 (3.6)	0
Deaths, N (%)	0	0	0	0	0	1 (0.3)	[redacted]	[redacted]	0	0

ADA = adalimumab; AE = adverse event; CI = confidence interval; DLQI = Dermatology Life Quality Index; ITT = intention-to-treat; LOCF = last observation carried forward; LS = least squares; NR = not reported; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; PSS = Psoriasis Symptoms Scale; RZB = risankizumab; SAE = serious adverse event; SE = standard error; sPGA = static Physician Global Assessment; UST = ustekinumab; vs. = versus; WDAE = withdrawal due to adverse event.

Note: In all studies, Part A is from week 0 to 16. In UltIMMA-1 and UltIMMA-2, Part B is from week 16 to 52. IMMhance is ongoing and data for Part B is from week 28 to 52. In IMMvent, Part B is from week 16 to 44.

[a] For Part A, CI and *P* values are computed for comparison between RZB versus UST, and RZB versus PBO. Across the strata, the 95% CI for adjusted difference was calculated according to the Cochran–Mantel–Haenszel test adjusted for the comparison of two treatment groups. If there was a stratum containing zero count, 0.1 was added to each cell. Within each stratum, the 95% CI for the difference was calculated based on normal approximation to the binomial distribution. Across the strata; *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata.

[b] $P < 0.001$.

[c] The ITT_B_R population for IMMhance included patients randomized to risankizumab (arm 1) in Part A and re-randomized to risankizumab or placebo in Part B.

[d] The ITT_B_RR population for IMMvent included all patients randomized to adalimumab at baseline in Part A who were re-randomized at week 16.

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Introduction

Disease Prevalence and Incidence

Plaque psoriasis is a chronic, inflammatory skin disease caused in part by dysregulation of the immune system. It is a T-cell–mediated disease driven primarily by pathogenic T-cells that produce high levels of interleukin 17 (IL-17) and tumour necrosis factor (TNF) alpha in response to interleukin 23 (IL-23).[1]

Psoriasis is characterized by the presence of erythematous inflammatory plaques that may be itchy or painful and are usually covered by silver, flaking scales.[1,2] In addition to the overt dermatological symptoms, plaque psoriasis is often associated with psychosocial symptoms, including poor self-esteem, and may affect various aspects of social functioning, including interpersonal relationships and performance at school or work.[2] According to patient input received for this CADTH Common Drug Review (CDR), one-third of participants indicated loss of sleep, negative effects on self-confidence, and problems with intimacy, and 47% indicated that concentration at work was frequently affected. Psoriasis is associated with comorbid conditions, including depressive symptoms, conditions associated with an increased risk of cardiovascular disease (such as type 2 diabetes, metabolic syndrome, coronary heart disease, and obesity), psoriatic arthritis, and kidney disease.[24-29] The extent to which symptoms and risk factors impact the patient's daily life may depend on the severity of the disease.[24,30]

The severity of psoriasis is classified as either mild, moderate, or severe using criteria such as body surface area (BSA) or scores on the Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI). Using these measures, moderate psoriasis involves a PASI score of 8 or higher, and severe psoriasis can be defined as PASI ≥ 10 or DLQI ≥ 10 or BSA ≥ 10%. Although clear definitions of psoriasis severity can be applied to clinical trials, variability exists in clinical practice. According to the clinical expert consulted for this Clinical Study Report, in clinical practice, disease severity is determined based on the severity and extent of lesions, and the extent to which the condition impacts patient health-related quality of life (HRQoL) and activities of daily living, but may vary across physicians and depends largely on the patient's input. As per the Canadian Guidelines for the Management of Plaque Psoriasis, the definition of moderate or severe psoriasis for clinical practice is when it significantly affects patient HRQoL due to the degree of physical discomfort caused by the condition or location of manifestation, or when the condition causes severe degradation in HRQoL and cannot be controlled by routine skin-care measures or topical therapy.[6]

It is estimated that approximately one million Canadians are living with psoriasis.[3] Plaque psoriasis is the most common form and represents approximately 90% of cases.[3] Approximately 35% of patients with psoriasis have moderate to severe disease.[4]

Standards of Therapy

Due to the chronic nature of the condition, plaque psoriasis requires lifelong treatment. Measures of treatment success include clearance (absence of signs of disease), control (satisfactory response to therapy as defined by the patient or physician), and remission (suppression of signs and symptoms over time).[6] Clearance and symptom control have been identified as treatment outcomes that are important to patients. According to the

clinical expert, treatment decisions depend largely on the patient's perception of their disease.

Topical treatments (such as corticosteroids, vitamin D3 analogues, retinoids, anthralin, and tars) may be used in patients with moderate to severe psoriasis, but it is widely accepted that they will not be sufficient to control symptoms in this patient population.[5,6] Treatment for moderate to severe plaque psoriasis often involves systemic therapies. Traditional systemic drugs include cyclosporine and methotrexate, but long-term use is limited by toxicity.[6] Biologic drugs are appropriate for long-term use and are generally associated with evidence of disease clearance within three months of initiating treatment.[2] According to the clinical expert consulted for this review, in patients who fail to respond to treatment with one biologic, the dose may be increased or patients may be switched to another biologic. It is estimated that approximately 20% of patients will discontinue treatment with a biologic;[31-36] however, according to the clinical expert consulted for this review, discontinuation rates are lower in Canada due to the clinical practice of increasing the dose of the biologic in patients who do not exhibit an adequate response. The first biologic drugs approved to treat plaque psoriasis were TNF-alpha inhibitors and include adalimumab, etanercept, and infliximab. While effective and associated with rapid disease control, these TNF-alpha inhibitors are associated with a number of overlapping safety concerns, including serious infections (e.g., sepsis, reactivated tuberculosis, viral infections), autoimmune conditions (e.g., lupus and demyelinating disorders), and malignancies such as lymphoma.[5,6] Newer biologic drugs include the IL-23 inhibitor guselkumab, the IL-12/23 inhibitor ustekinumab, and IL-17 inhibitors secukinumab, ixekizumab, and brodalumab. However, their use is associated with serious infections, potential activation of inflammatory bowel disease in the case of IL-17 inhibitors, and suicidal ideation in the case of brodalumab.[7-17] According to the clinical expert consulted for this review, IL-17 and IL-23 inhibitors have replaced the TNF-alpha inhibitors as the most commonly used biologic treatments in Canada. In the patient input received for this review, patients expressed concern regarding the side effects of currently available treatments and a desire for a treatment with fewer side effects. The most recent update to the Canadian treatment guidelines was published in 2016 and does not include these recently approved biologic treatments. No international guidelines incorporating these biologic drugs were identified; however, CADTH and the National Institute for Health and Care Excellence (NICE) have issued recommendations that each of these drugs be reimbursed with conditions. Table 2 provides an overview of the biologic drugs for the treatment of plaque psoriasis in Canada.

Drug

Risankizumab (Skyrizi) is a solution for injection in a single-use, pre-filled syringe containing 75 mg risankizumab in 0.83 mL (90 mg/mL) sterile solution. Risankizumab is approved by Health Canada for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[37] Risankizumab is not indicated in the pediatric population, as the efficacy and safety of risankizumab have not been evaluated in patients less than 18 years of age. The recommended dose of risankizumab is 150 mg (two 75 mg injections) administered by subcutaneous (SC) injection at week 0, week 4, and every 12 weeks thereafter.[37]

Risankizumab is a humanized immunoglobulin G1 monoclonal antibody that selectively binds with high affinity to the p19 subunit of human IL-23 cytokine and inhibits IL-23 signalling in cell-based assays, including the release of the pro-inflammatory cytokine, IL-17.[37]

Table 2: Key Characteristics of Biologic Drugs for the Treatment of Psoriasis

Biologic	Indication[a]	Route of Administration	Recommended Dose	Serious Side Effects/Safety Issues
IL-23 Inhibitors				
Risankizumab	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	SC	150 mg (two 75 mg injections) administered by subcutaneous injection at week 0 and week 4, and every 12 weeks thereafter	Infection Hypersensitivity reactions
Guselkumab (Tremfya)	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	SC	100 mg administered at week 0 and week 4, followed by maintenance dosing every 8 weeks thereafter	Infection
IL-12/23 Inhibitors				
Ustekinumab (Stelara)	In adult patients for the treatment of chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy Treatment of chronic moderate to severe plaque psoriasis in adolescent patients from 12 to 17 years of age who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies Consideration should be given to discontinuing treatment in patients who have shown no response up to 12 weeks of treatment	SC	45 mg at weeks 0 and 4, then every 12 weeks thereafter Alternatively, 90 mg may be used in patients with a body weight > 100 kg For patients who inadequately respond to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks Dose of 0.75 mg/kg is recommended in pediatric patients weighing < 60 kg	Infection Malignancy Serious hypersensitivity reactions
IL-17 inhibitors				
Brodalumab (Siliq)	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy	SC	210 mg at weeks 0, 1, and 2 followed by 210 mg every 2 weeks	• Suicidal ideation and behaviour • Crohn's disease • Infection
Secukinumab (Cosentyx)	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy	SC	300 mg with initial dosing at weeks 0, 1, 2, 3, and 4 followed by monthly maintenance dosing	• Infection • Inflammatory bowel disease • Serious hypersensitivity reactions •
Ixekizumab (Taltz)	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	SC	160 mg at week 0 followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks	• Infection • Serious hypersensitivity reactions • Inflammatory bowel disease
TNF inhibitors				

Biologic	Indication[a]	Route of Administration	Recommended Dose	Serious Side Effects/Safety Issues
Infliximab (Remicade, Inflectra, Renflexis)	Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy For patients with chronic moderate plaque psoriasis, infliximab should be used after phototherapy has been shown to be ineffective or inappropriate	IV	5 mg/kg followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter If a patient does not show an adequate response at week 14 after infusions at weeks 0, 2, and 6, no additional treatment with infliximab should be given	• Infection • Malignancies Cardiovascular events • Hematologic abnormalities • Hepatic abnormalities • Hypersensitivity reactions • Autoimmunity and immunogenicity • Neurologic events
Adalimumab (Humira, Hadlima)	Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy For patients with chronic moderate plaque psoriasis, adalimumab should be used after phototherapy has been shown to be ineffective or inappropriate	SC	Initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period	• Malignancies • Infection • Congestive heart failure • Hematologic events • Hypersensitivity reactions • Autoimmunity and immunosuppressi on • Neurologic events
Etanercept (Enbrel[b])	Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy Treatment of pediatric patients aged 4 to 17 years with chronic severe psoriasis who are candidates for systemic therapy or phototherapy	SC	Adults: Starting dose of 50 mg dose given twice weekly (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of 50 mg per week. A maintenance dose of 50 mg given twice weekly has also been shown to be efficacious Pediatric patients: 0.8 mg/kg per week (up to a maximum of 50 mg per week)	• Infections • Malignancies • Neurologic events • Hematologic events • Congestive heart failure • Autoimmunity

IL = interleukin; IV = intravenous; SC = subcutaneous.

[a] Health Canada indication.

[b] Biosimilar etanercept products are not approved by Health Canada for the treatment of plaque psoriasis.

Source: Product monographs for Skyrizi,[37] Tremfya,[7] Stelara,[8] Siliq,[9] Cosentyx,[10] Taltz,[11] Remicade,[12] Inflectra,[13] Renflexis,[14] Humira,[15] Hadlima,[17] and Enbrel.[16]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of risankizumab solution for injection in a pre-filled syringe (75 mg risankizumab in 0.83 mL solution; 90 mg/mL) for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adults with moderate to severe plaque psoriasis **Subgroups:** • disease severity • biologic naive vs. biologic experienced • systemic naive vs. systemic exposed • body weight (≤ 100 kg vs. > 100 kg)
Intervention	Risankizumab alone or in combination with other therapies: 150 mg administered by SC injection at week 0, week 4, and every 12 weeks thereafter
Comparators	When used as monotherapy or as combination therapy with other non-biologic drugs: **Biologic drugs targeting interleukins:** • brodalumab, guselkumab, ixekizumab, secukinumab, ustekinumab ***Biologic drugs targeting TNF alpha:*** • adalimumab, etanercept, infliximab **Non-biologic systemic drugs:** • acitretin, apremilast, cyclosporine, methotrexate
Outcomes	**Efficacy outcomes:** • HRQoL by a validated instrument (e.g., DLQI, SF-36, EQ-5D)[a] • skin clearance / psoriasis score (e.g., PASI response, global assessment)[a] • patient-reported outcomes (e.g., PSI)[a] **Harms outcomes:** AEs,[a] SAEs, WDAEs, mortality, notable harms (including infections, injection-site reactions, hypersensitivity events, immunogenicity, inflammatory bowel disease, major cardiovascular events, psychiatric symptoms)
Study Design	Published and unpublished phase III and IV RCTs

AE = adverse event; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions questionnaire; HRQoL = health-related quality of life; PASI = Psoriasis Area and Severity Index; PSI = Psoriasis Symptom Inventory; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; WDAE = withdrawal due to adverse event; vs. = versus.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Skyrizi (risankizumab).

No methodological filters were applied to limit retrieval to study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 16, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on March 20, 2019. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, and databases. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4, excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

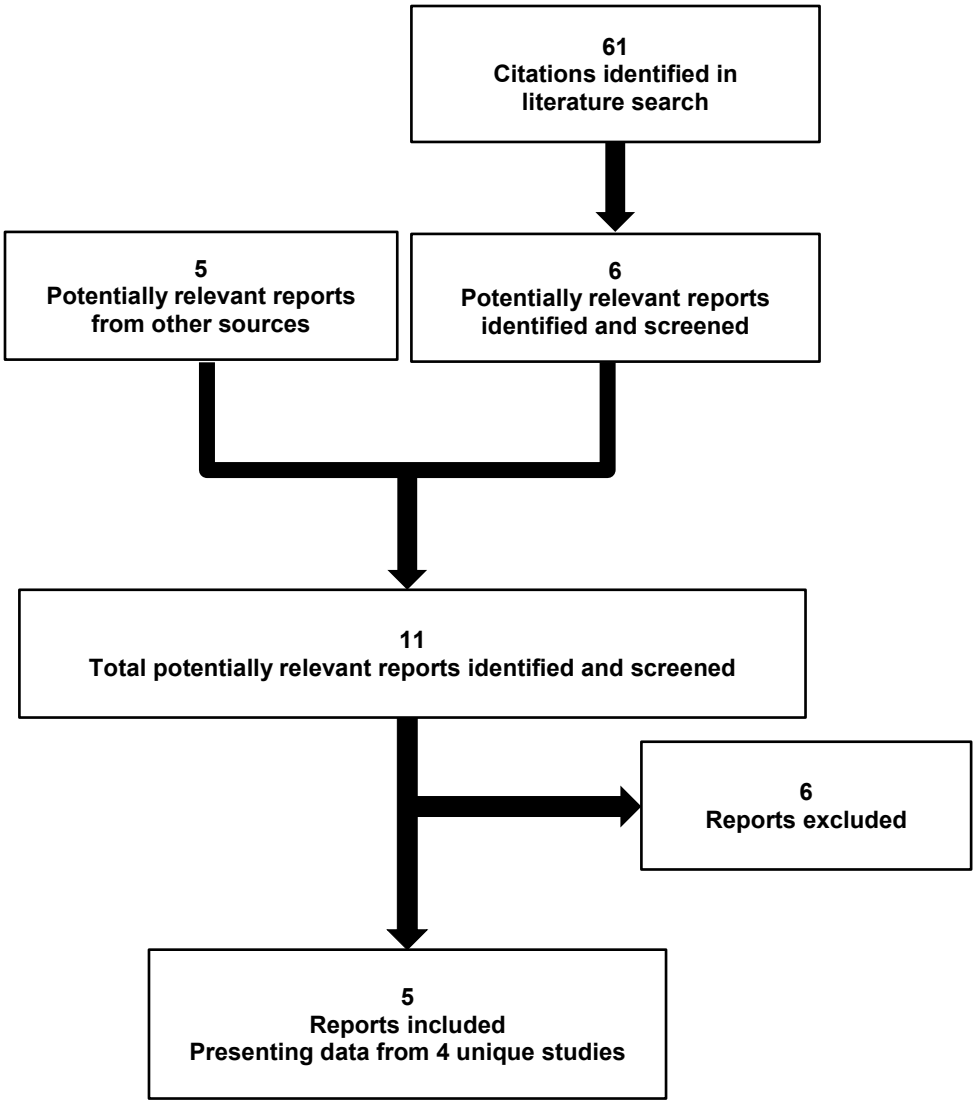


Table 4: Details of Included Studies

		UltIMMA-1 (M16-008)	UltIMMA-2 (M15-995)	IMMhance (M15-992)	IMMvent (M16-010)
Designs and Populations	**Study Design**	Double-blind, double-dummy and placebo- and active-controlled phase III RCT		Double-blind, placebo-controlled phase III RCT (ongoing)	Double-blind, double-dummy, active-controlled phase III RCT
	Locations	79 sites, 8 countries (Australia, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, US)	64 sites, 10 countries (Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, US)	60 sites, 9 countries (Australia, Belgium, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, US)	66 sites, 11 countries (Canada, Czech Republic, Finland, France, Germany, Mexico, Poland, Portugal, Sweden, Taiwan, US)
	Randomized (N)	506	491	507	605
	Inclusion Criteria	• ≥ 18 years of age • Moderate to severe chronic plaque psoriasis of ≥ 6 months duration with or without PsA • BSA involvement ≥ 10% • PASI ≥ 12 • sPGA ≥ 3 • Candidates for systemic therapy or phototherapy • Candidates for treatment with ustekinumab		• ≥ 18 years of age • Moderate to severe chronic plaque psoriasis of ≥ 6 months duration • BSA involvement ≥ 10% • PASI ≥ 12 • sPGA ≥ 3 • Candidates for systemic therapy or phototherapy	• ≥ 18 years of age • Moderate to severe chronic plaque psoriasis of ≥ 6 months duration with or without PsA • BSA involvement ≥ 10% • PASI ≥ 12 • sPGA ≥ 3 • Candidates for systemic therapy or phototherapy • Candidates for treatment with adalimumab
	Exclusion Criteria	• Non-plaque forms of psoriasis • Current drug-induced psoriasis • Active ongoing inflammatory diseases other than psoriasis • Chronic or relevant acute infections (HIV, hepatitis, TB) • Documented active or suspected malignancy or history of malignancy within 5 years prior to screening • Previous exposure to risankizumab or ustekinumab		• Non-plaque forms of psoriasis • Current drug-induced psoriasis • Active ongoing inflammatory diseases other than psoriasis • Chronic or relevant acute infections (HIV, hepatitis, TB) • Documented active or suspected malignancy or history of malignancy within 5 years prior to screening • Previous exposure to risankizumab	• Non-plaque forms of psoriasis • Current drug-induced psoriasis • Active ongoing inflammatory diseases other than psoriasis • Chronic or relevant acute infections (HIV, hepatitis, TB) • Documented active or suspected malignancy or history of malignancy within 5 years prior to screening • Previous exposure to risankizumab or adalimumab
Drugs	**Intervention**	150 mg risankizumab SC at weeks 0 and 4, every 12 weeks thereafter up to week 40		150 mg risankizumab SC at weeks 0 and 4, every 12 weeks thereafter up to week 88	150 mg risankizumab SC at weeks 0 and 4, every 12 weeks thereafter up to week 32

		UltIMMA-1 (M16-008)	UltIMMA-2 (M15-995)	IMMhance (M15-992)	IMMvent (M16-010)
	Comparator(s)	*Part A*: Ustekinumab (45 mg for patients ≤ 100 kg; 90 mg for patients > 100 kg) or placebo SC at weeks 0 and 4 *Part B*: Ustekinumab (45 mg for patients ≤ 100 kg; 90 mg for patients > 100 kg) at weeks 16, 28, 40		Placebo SC at weeks 0 and 4 and every 12 weeks thereafter up to week 88	Adalimumab SC; 80 mg at randomization, 40 mg at weeks 1 and every other week up to week 41
DURATION	**Phase**				
	Screening	1 to 6 weeks		up to 6 weeks	1 to 6 weeks
	Treatment period	*Part A*: 16 weeks *Part B*: week 16 to 52		*Part A1*: 16 weeks *Part A2*: Up to week 28 *Part B*: week 28 to 88	*Part A*: 16 weeks *Part B*: week 16 to 44
	Follow-up	12 to 16 weeks		16 weeks	16 weeks
OUTCOMES	**Primary End Point**	• PASI 90 at week 16 • sPGA of clear or almost clear at week 16		• PASI 90 at week 16 • sPGA of clear or almost clear at week 16	• PASI 90 at week 16 • sPGA of clear or almost clear at week 16
	Other End Points	• PASI 100 • PASI 90 • PASI 75 • sPGA of clear (0) • sPGA of clear or almost clear (0 or 1) • DLQI • PSS score		• PASI 75 • PASI 100 • sPGA of clear or almost clear (0 or 1) • sPGA of clear (0) • DLQI	• PASI 75 • PASI 100 • PASI 90 • sPGA of clear or almost clear (0 or 1) • sPGA of clear (0) • DLQI
NOTES	**Publications**	Gordon et al., 2018[38]		NA	NA

BSA = body surface area; DLQI = Dermatology Life Quality Index; NA = not available; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PSS = Psoriasis Symptoms Scale; RCT = randomized controlled trial; SC = subcutaneous; sPGA = static Physician Global Assessment; TB = tuberculosis.

Note: One additional report was included (CDR submission).[39]

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Included Studies

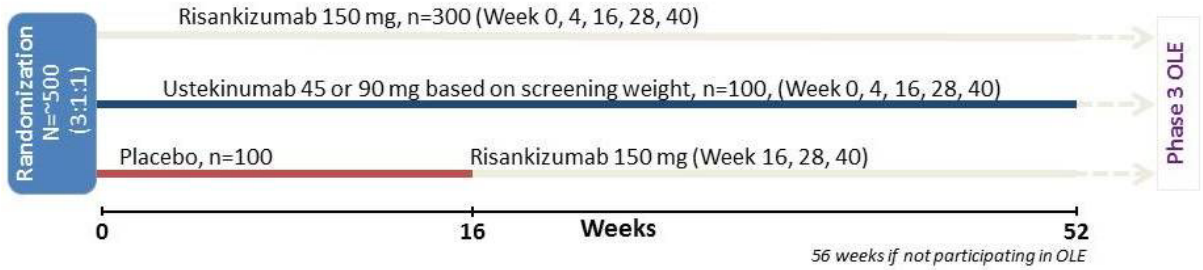
Description of Studies

A total of four phase III randomized controlled trials (RCTs) were included in the CDR systematic review: UltIMMA-1 (N = 506), UltIMMA-2 (N = 491), IMMhance (N = 507), and IMMvent (N = 605). All four trials had similar inclusion and exclusion criteria and enrolled patients with moderate to severe plaque psoriasis (Table 4). All four trials were conducted in two parts (A and B); treatment duration and co-primary end points were identical in Part A of each study. In each study, patients were randomized to double-blind treatment in blocks and stratified by body weight (≤ 100 kg versus > 100 kg) and prior exposure to TNF antagonists. Eligible patients from each of the studies had the option of participating in the open-label extension study M15-997 (described in Appendix 6).

UltIMMA-1 and UltIMMA-2 were identically designed multi-centre, randomized, double-blind, double-dummy, placebo-controlled, active comparator–controlled studies completed in 2017 that were designed to assess the efficacy and safety of risankizumab versus placebo and ustekinumab. UltIMMA-1 was conducted in 79 sites across eight countries,

including nine sites in Canada. UltIMMA-2 was conducted in 64 sites across 10 countries, including eight sites in Canada. The studies consisted of two parts, as depicted in Figure 2. Part A (week 0 to 16) was a 16-week double-blind treatment period in which patients were randomized using interactive response technology in a 3:1:1 ratio to treatment with either risankizumab (150 mg SC), ustekinumab (45 mg or 90 mg SC for patients ≤ 100 kg or > 100 kg, respectively) or placebo SC at weeks 0 and 4. In Part B (week 16 to 52), all patients randomized to placebo in Part A were switched to treatment with risankizumab (150 mg every 12 weeks), while patients randomized to risankizumab or ustekinumab continued their assigned treatment (risankizumab every 12 weeks or ustekinumab at weeks 16, 28, and 40) up to week 40 and were followed up to week 52. At week 52, eligible patients had the option of participating in the open-label extension study M15-997 (described in Appendix 6).

Figure 2: UltIMMA-1 and UltIMMA-2 Study Design



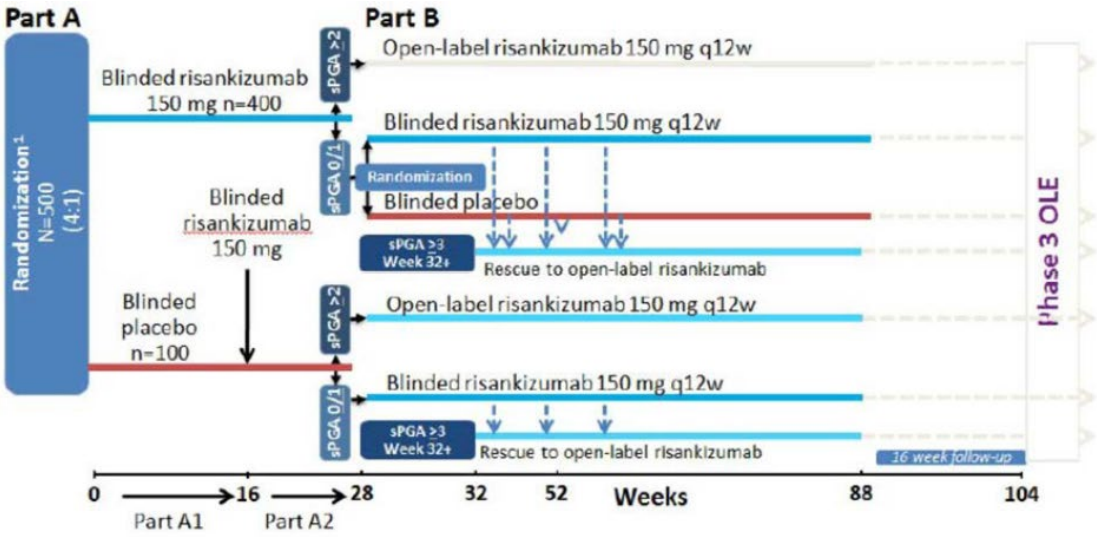
OLE = open-label extension.

Source: UltIMMA-1[20] and UltIMMA-2[21] Clinical Study Reports.

IMMhance was a multi-centre, randomized, double-blind, placebo-controlled, ongoing trial designed to evaluate the safety and efficacy of risankizumab versus placebo, maintenance of response to risankizumab following drug withdrawal, and response following re-treatment with risankizumab in patients who experienced relapse after withdrawal. An interim analysis up to week 52 was available for this review (September 1, 2017 cut-off date). IMMhance is being conducted in 60 sites across nine countries, including nine sites in Canada. The IMMhance study design is illustrated in Figure 3. In Part A1 (week 0 to 16), patients were randomized in a 4:1 ratio to either risankizumab 150 mg (arm 1) or placebo (arm 2) SC at weeks 0 and 4, up to week 16. At week 16 (Part A2), all patients originally randomized to placebo received treatment with risankizumab 150 mg SC every 12 weeks. Note that patients in this treatment arm did not receive the induction regimen for risankizumab. Therefore, results pertaining to arm 2 of this study are not described in this CDR review, as the dosing for risankizumab is not aligned with the recommended dosing described in the Health Canada product monograph or the CDR review protocol. Patients originally randomized to risankizumab (arm 1) continued their treatment every 12 weeks up to week 28 (beginning of Part B), at which time all patients were assessed for response to risankizumab based on the static Physician Global Assessment (sPGA). Patients who had an sPGA ≥ 2 at week 28 were considered nonresponders and received open-label treatment with risankizumab 150 mg SC every 12 weeks up to week 88. Patients who had an sPGA of clear (0) or almost clear (1) at week 28 were re-randomized in a 1:2 ratio to continue treatment with risankizumab 150 mg or placebo SC every 12 weeks up to week 88; blinding was maintained during this part of the study. After week 32, all re-randomized patients who experienced relapse were switched to open-label treatment with risankizumab

and re-treated with risankizumab 150 mg at 0, 4, and 16 weeks after relapse (as time permitted during the treatment period of Part B).

Figure 3: IMMhance Study Design



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

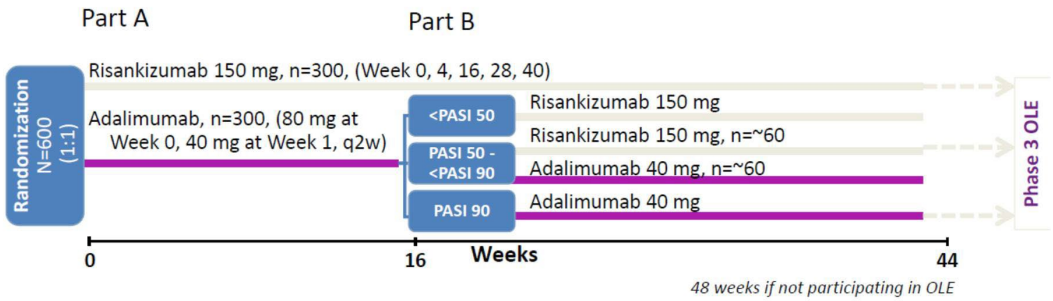
Source: IMMhance Clinical Study Report.[22]

IMMvent was a multi-centre, randomized, double-blind, double-dummy, active-controlled trial completed in 2017 designed to assess the efficacy and safety of risankizumab versus adalimumab (Part A, weeks 0 to 16), and to assess the efficacy and safety of switching to risankizumab in patients who had an inadequate response to adalimumab versus continuing treatment with adalimumab (Part B, week 16 to 44). IMMvent was conducted in 66 sites across 11 countries, including seven sites in Canada. The IMMvent study design is illustrated in Figure 4. In Part A, patients were randomized in a 1:1 ratio to either risankizumab (150 mg at weeks 0 and 4) or adalimumab (80 mg at randomization, and 40 mg starting at week 1 and every other week thereafter) SC up to week 16. At week 16, patients who were randomized to adalimumab in Part A were reassigned to one of the following treatment groups, based on PASI score at week 16:

- PASI < 50: switched to treatment with risankizumab 150 mg SC at weeks 16, 20 (induction regimen), and 32
- PASI 90: continued treatment with adalimumab 40 mg SC every other week through week 41
- PASI 50 to < 90: re-randomized 1:1 to either risankizumab 150 mg SC at weeks 16, 20 (induction regimen), and 32, or continued treatment with adalimumab 40 mg SC every other week through week 41.

All patients who were randomized to risankizumab in Part A continued on risankizumab (150 mg SC every 12 weeks) through week 44.

Figure 4: IMMvent Study Design



OLE = open-label extension; PASI = Psoriasis Area and Severity Index; q2w = every 2 weeks.

Source: IMMvent Clinical Study Report.[23]

Populations

Inclusion and Exclusion Criteria

Key inclusion and exclusion criteria were similar for all four trials. Please refer to Table 4 for a list of key inclusion and exclusion criteria for each included trial.

All trials included patients with moderate to severe plaque psoriasis defined as BSA involvement of ≥ 10%, PASI ≥ 12, and sPGA ≥ 3, which is aligned with definitions of disease severity used in clinical trials in the Canadian Guidelines for the Management of Plaque Psoriasis.[6] Patients were eligible for study participation regardless of prior treatment status (i.e., those naive or experienced with phototherapy, traditional systemic treatments, or biologic treatments); only those who had previously been exposed to any study drug (i.e., risankizumab, ustekinumab, or adalimumab) were excluded. Other patients who were ineligible for study participation included various groups of patients with comorbid conditions (those with current or a history of malignant disease or chronic or relevant acute infections) and those with forms of psoriasis other than plaque psoriasis.

Baseline Characteristics

The baseline demographics and disease characteristics at the beginning of Part A for each of the trials are summarized in Table 5. Overall, baseline demographics were similar across the trials as well as between the treatment groups within trials. In each of the studies, the majority of participants were male (68% to 77%) and white (65% to 92%). The mean age of patients across the four trials was between 45 and 49 years and the mean weight of patients ranged from 88 kg to 92 kg, with two-thirds of patients in each study weighing less than 100 kg. UltIMMA-1 included a higher percentage of Asian patients, given the location of study sites; therefore, the mean body weight of patients in this trial is slightly lower than in UltIMMA-2, IMMhance, and IMMvent.

Baseline patient disease characteristics were consistent with a population with moderate to severe plaque psoriasis and were generally comparable between treatment groups across the four trials. The majority of patients (77% to 85%) had a baseline sPGA score of 3 (moderate), a mean PASI score between 18 and 21, and BSA involvement of 21% to 28%. There was a slight imbalance in PASI score in UltIMMA-2, where patients in the risankizumab group had a slightly higher mean PASI score and higher BSA involvement at baseline (PASI: 20.54; BSA: 26.2%) than patients in the placebo (PASI: 18.86; BSA: 23.9%) and ustekinumab (PASI: 18.21; BSA: 20.9%) groups.

Previous treatment experience varied across and within studies. A higher number of patients in each treatment group in UltIMMA-1 had previous experience with phototherapy or photochemotherapy compared with the other three trials. In each of the trials, approximately half the patients had used traditional systemic therapy (36.7% to 57.8%); however, as shown in Table 5, this was not balanced across treatment groups in UltIMMA-1, UltIMMA-2, and IMMhance. Biologics were used previously by 30% to 57% of patients across the trials; although previous exposure to biologic treatment varied across trials, this was well balanced between treatment groups within each study except for UltIMMA-1, where the proportion of patients previously treated with a biologic ranged from 30% in the ustekinumab group to 39.2% in the placebo group.

Baseline characteristics were not summarized for the intention-to-treat (ITT) population in Part B in UltIMMA-1 or UltIMMA-2. In Part B, patients initially randomized to placebo were switched to treatment with risankizumab 150 mg SC every 12 weeks starting at week 16; otherwise, randomization was maintained within the risankizumab and ustekinumab treatment groups. Given that patient demographics and baseline characteristics were generally well balanced between the risankizumab and ustekinumab treatment groups in Part A, and given the low rate of study withdrawal from Part A and the high proportion of patients dosed in Part B (Table 10 and Table 11), baseline characteristics for these treatment groups should be similar to Part A.

In IMMhance and IMMvent, demographic and disease characteristics for patients re-randomized in Part B were well balanced between groups and were generally similar to those in Part A (Table 6). In both studies, the re-randomized patient population consisted mostly of males and was predominantly white, with the majority of patients considered to be of moderate disease severity. In IMMhance, disease characteristics and previous treatment experience for patients re-randomized in Part B was similar to patients in Part A. In IMMvent, mean age was slightly higher for patients re-randomized to risankizumab (mean: 49.5 years; standard deviation [SD]: 14.75). Also of note was that the mean PASI score at the beginning of Part B appeared to be lower in the risankizumab group. Further, more patients re-randomized to the risankizumab group (60.4%) had previous experience with traditional systemic therapy than those re-randomized to the adalimumab group (41.1%).

Table 5: Summary of Baseline Characteristics, Part A (Intention-to-Treat Population)

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
Title	**PBO (N = 102)**	**UST (N = 100)**	**RZB (N = 304)**	**PBO (N = 98)**	**UST (N = 99)**	**RZB (N = 294)**	**PBO (N = 100)**	**RZB (N = 407)**	**ADA (N = 304)**	**RZB (N = 301)**
Mean age, years (SD)	49.3 (13.63)	46.5 (13.42)	48.3 (13.39)	46.3 (13.26)	48.6 (14.81)	46.2 (13.68)	47.9 (13.78)	49.6 (13.17)	47.0 (13.09)	45.3 (13.79)
Sex, n (%)										
Female	23 (22.5)	30 (30.0)	92 (30.3)	31 (31.6)	33 (33.3)	91 (31.0)	27 (27.0)	124 (30.5)	92 (30.3)	91 (30.2)
Male	79 (77.5)	70 (70.0)	212 (69.7)	67 (68.4)	66 (66.7)	203 (69.0)	73 (73.0)	283 (69.5)	212 (69.7)	210 (69.8)
Race, n (%)										
White	71 (69.6)	74 (74.0)	200 (65.8)	87 (88.8)	91 (91.9)	255 (86.7)	82 (82.0)	320 (78.6)	263 (86.5)	245 (81.4)
Black	1 (1.0)	1 (1.0)	10 (3.3)	2 (2.0)	2 (2.0)	10 (3.4)	2 (2.0)	18 (4.4)	6 (2.0)	11 (3.7)
Asian	28 (27.5)	22 (22.0)	86 (28.3)	7 (7.1)	4 (4.0)	25 (8.5)	15 (15.0)	64 (15.7)	35 (11.5)	41 (13.6)
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multi-race	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg										
Mean (SD)	88.82 (20.227)	88.89 (22.875)	87.81 (22.897)	92.15 (20.007)	91.85 (21.439)	92.20 (21.727)	91.14 (20.176)	92.17 (23.556)	91.35 (24.580)	88.79 (23.117)
Median (min, max)	84.10 (53.2, 144.2)	85.35 (43.5, 157.2)	83.90 (45.0, 160.8)	90.00 (48.0, 157.0)	89.50 (46.0, 143.5)	90.40 (46.0, 170.0)	92.40 (51.7, 137.3)	88.60 (47.0, 193.1)	87.00 (42.6, 190.0)	86.00 (43.2, 163.2)
≤ 100 kg, n (%)	76 (74.5)	74 (74.0)	226 (74.3)	67 (68.4)	69 (69.7)	203 (69.0)	68 (68.0)	283 (69.5)	217 (71.4)	219 (72.8)
> 100 kg, n (%)	26 (25.5)	26 (26.0)	78 (25.7)	31 (31.6)	30 (30.3)	91 (31.0)	32 (32.0)	124 (30.5)	87 (28.6)	82 (27.2)
PASI										
Mean (SD)	20.50 (6.681)	20.08 (6.837)	20.63 (7.675)	18.86 (7.308)	18.21 (5.857)	20.54 (7.831)	21.17 (8.682)	19.91 (7.935)	19.72 (7.512)	19.95 (7.459)

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
Title	**PBO (N = 102)**	**UST (N = 100)**	**RZB (N = 304)**	**PBO (N = 98)**	**UST (N = 99)**	**RZB (N = 294)**	**PBO (N = 100)**	**RZB (N = 407)**	**ADA (N = 304)**	**RZB (N = 301)**
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSA (%)										
Mean (SD)	27.9 (17.23)	25.2 (14.70)	26.2 (15.35)	23.9 (15.70)	20.9 (12.07)	26.2 (15.94)	28.3 (19.07)	25.6 (17.02)	25.5 (16.77)	26.5 (16.48)
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sPGA, n (%)										
Moderate	86 (84.3)	85 (85.0)	256 (84.2)	77 (78.6)	81 (81.8)	228 (77.6)	[redacted]	[redacted]	[redacted]	[redacted]
Severe	16 (15.7)	15 (15.0)	48 (15.8)	21 (21.4)	18 (18.2)	66 (22.4)	23 (23.0)	84 (20.6)	58 (19.1)	58 (19.3)
PsA Status, n (%)										
Diagnosed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suspected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV Disease, n (%)										
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transient ischemic attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topical therapy, n (%)							[redacted]	[redacted]	[redacted]	[redacted]
Phototherapy or photochemotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
Title	**PBO (N = 102)**	**UST (N = 100)**	**RZB (N = 304)**	**PBO (N = 98)**	**UST (N = 99)**	**RZB (N = 294)**	**PBO (N = 100)**	**RZB (N = 407)**	**ADA (N = 304)**	**RZB (N = 301)**
Non-biologic systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any biologic, n (%)	40 (39.2)	30 (30.0)	104 (34.2)	42 (42.9)	43 (43.4)	118 (40.1)	51 (51.0)	230 (56.5)	111 (36.5)	118 (39.2)
Naive to systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Naive to all (other than topical treatment), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; BSA = body surface area; CV = cardiovascular; ITT = intention-to-treat; max = maximum; min = minimum; PASI = Psoriasis Area and Severity Index; PBO = placebo; PsA = psoriatic arthritis; RZB = risankizumab; SD = standard deviation; sPGA = static Physician Global Assessment; UST = ustekinumab.

Note: ITT population refers to Part A (weeks 0 to 16) in all studies.

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Table 6: Summary of Baseline Characteristics, Part B (Intention-to-Treat Population)

Title	IMMhance (ITT_B_R Population)[a]		IMMvent (ITT_B_RR Population)[a]	
	RZB/RZB/ PBO (N = 225)	RZB/RZB/ RZB (N = 111)	ADA/ADA (N = 56)	ADA/RZB (N = 53)
Mean age, years (SD)	49.3 (13.05)	48.2 (13.44)	45.8 (11.33)	49.5 (14.75)
Sex, n (%)				
Female	69 (30.7)	28 (25.2)	16 (28.6)	18 (34.0)
Male	156 (69.3)	83 (74.8)	40 (71.4)	35 (66.0)
Race, n (%)				
White	177 (78.7)	82 (73.9)	44 (78.6)	42 (79.2)
Black	10 (4.4)	6 (5.4)	0	1 (1.9)
Asian	34 (15.1)	23 (20.7)	12 (21.4)	10 (18.9)
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]
Multi-race	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg				
Mean (SD)	91.01 (22.199)	91.35 (23.674)	92.56 (25.033)	89.39 (25.897)
Median (min, max)	88.00 (47.2, 159.4)	87.10 (47.0, 164.3)	[redacted]	[redacted]
≤ 100 kg, n (%)	159 (70.7)	79 (71.2)	40 (71.4)	40 (75.5)
> 100 kg, n (%)	66 (29.3)	32 (28.8)	16 (28.6)	13 (24.5)
PASI				
Mean (SD)	19.67 (7.304)	20.25 (8.879)	19.25 (7.613)	[redacted]
Median (min, max)	17.40 (12.0, 47.6)	17.00 (12.0, 63.4)	[redacted]	[redacted]
BSA (%)				
Mean (SD)	25.4 (15.67)	25.2 (17.64)	24.3 (16.43)	27.6 (19.89)
Median (min, max)	20.0 (10, 84)	19.0 (10, 90)	[redacted]	[redacted]
sPGA, n (%)				
Moderate	185 (82.2)	86 (77.5)	[redacted]	[redacted]
Severe	40 (17.8)	25 (22.5)	13 (23.2)	6 (11.3)
PsA Status, n (%)				
Diagnosed	[redacted]	[redacted]	[redacted]	[redacted]
Suspected	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
CV Disease, n (%)				
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]
Transient ischemic attack	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]
Topical therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Title	IMMhance (ITT_B_R Population)[a]		IMMvent (ITT_B_RR Population)[a]	
	RZB/RZB/ PBO (N = 225)	RZB/RZB/ RZB (N = 111)	ADA/ADA (N = 56)	ADA/RZB (N = 53)
Phototherapy or photochemotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-biologic systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any biologic, n (%)	125 (55.6)	57 (51.4)	24 (42.9)	16 (30.2)
Naive to systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Naive to all (other than topical treatment), n (%)	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; BSA = body surface area; CV = cardiovascular; ITT = intention-to-treat; max = maximum; min = minimum; PASI = Psoriasis Area and Severity Index; PBO = placebo; PsA = psoriatic arthritis; RZB = risankizumab; SD = standard deviation; sPGA = static Physician Global Assessment; UST = ustekinumab.

[a] Baseline characteristics are for patients re-randomized in Part B. In IMMhance, the ITT_B_R population included patients who were considered responders to risankizumab and re-randomized to continue risankizumab or switch to placebo. In IMMvent, the ITT_B_RR population included patients initially randomized to adalimumab in Part A and re-randomized to either adalimumab or risankizumab in Part B.

Source: IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Interventions

In all of the four trials included in this review, risankizumab 150 mg for SC administration was provided in two pre-filled syringes, each containing 75 mg risankizumab. All comparative treatments were administered as per the product label. A placebo was administered SC using a pre-filled syringe. Matching placebos for the active and comparative treatments were employed as applicable. Patients were not permitted to use any biologic treatment, any traditional systemic treatments (including methotrexate, cyclosporine, corticosteroids, cyclophosphamide, tofacitinib, apremilast, retinoids, fumarate), photochemotherapy, phototherapy, or any topical treatments throughout the duration of the study. Each of these medications was restricted for a specified period of time prior to randomization, depending on the treatment (Table 7). Patients were permitted to continue concomitant therapies for chronic conditions other than those specified in the exclusion criteria.

Table 7: General Overview of Restricted Medications

Medications	Restriction Duration
Guselkumab, tildrakizumab	Not allowed neither before nor during trial participation
Briakinumab, secukinumab, ustekinumab	6 months prior to randomization
Brodalumab, ixekizumab	4 months prior to randomization
• Adalimumab, infliximab • Investigational products for psoriasis (non-biologics)	12 weeks prior to randomization
• Etanercept • Live virus vaccinations	6 weeks prior to randomization
• Any investigational device or product (excludes psoriasis products) • Other systemic immunomodulating treatments, e.g., methotrexate, cyclosporine A, corticosteroids,[a] cyclophosphamide, tofacitinib, apremilast • Other systemic psoriasis treatments (e.g., retinoids, fumarates, any other drug known to possibly benefit psoriasis) • Photochemotherapy (e.g., PUVA)	30 days prior to randomization
• Phototherapy (e.g., UVA, UVB) • Topical treatment for psoriasis or any other skin condition (e.g., corticosteroids,[b] vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, alpha-hydroxy, fruit acids)	14 days prior to randomization

PASI = Psoriasis Area and Severity Index; PUVA = psoralen–ultraviolet A; UVA = ultraviolet A; UVB = ultraviolet B.

[a] No restriction on corticosteroids with only a topical effect (e.g., inhaled corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).

[b] Exception: Topical steroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to trial visit in which PASI is assessed.

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

In Part A of UltIMMA-1 and UltIMMA-2, patients were randomized in a 3:1:1 ratio to treatment with either risankizumab (150 mg), ustekinumab (45 mg or 90 mg SC for patients ≤ 100 kg or > 100 kg, respectively) or placebo at weeks 0 and 4. In Part B (week 16 to 52), all patients randomized to placebo in Part A were switched to treatment with risankizumab (150 mg at weeks 16, 28, and 40), while patients randomized to risankizumab or ustekinumab continued their assigned treatment (risankizumab every 12 weeks or ustekinumab at weeks 16, 28, and 40). Blinding was maintained throughout Part B of the studies. Patients originally assigned to placebo in Part A did not receive an induction regimen of risankizumab at the start of Part B. Patients assigned to the risankizumab or placebo groups also received matching placebo for ustekinumab, while patients assigned to ustekinumab also received matching placebo for risankizumab.

In Part A of the IMMhance study, patients were randomized in a 4:1 ratio to either risankizumab 150 mg (arm 1) or placebo (arm 2) SC at weeks 0 and 4. All patients received one additional dose of risankizumab 150 mg SC at week 16. As discussed previously in this review, details of interventions for Part B will be restricted to arm 1 (i.e., patients randomized to treatment with risankizumab in Part A). Details of treatment received for patients in arm 1 during Part B are as follows:

- Nonresponders (sPGA ≥ 2): Open-label risankizumab 150 mg SC every 12 weeks starting at week 28 and continuing to week 88

- Responders (sPGA 0 or 1): Re-randomized at week 28 to continue treatment with 150 mg risankizumab or switched to matching placebo SC every 12 weeks starting at week 28 and continuing to week 88.

All patients who experienced relapse during Part B (sPGA ≥ 3) received open-label treatment with risankizumab 150 mg SC. [redacted]

In Part A of the IMMvent study, patients were randomized in a 1:1 ratio to either risankizumab (150 mg at weeks 0 and 4) plus matched placebo for adalimumab, or adalimumab (80 mg at randomization, and 40 mg starting at week 1 and every other week thereafter) plus matched placebo for risankizumab SC through week 15. During Part B of the study, patients who were randomized to adalimumab in Part A were reassigned to one of the following treatment groups, based on their PASI score at week 16:

- < PASI 50: Switched to treatment with risankizumab 150 mg SC at weeks 16, 20 (induction regimen), and 32, plus matching placebo for adalimumab through week 41
- PASI 90: Continued treatment with adalimumab 40 mg SC every other week plus matching placebo for risankizumab through week 41
- PASI 50 to < PASI 90: re-randomized in a 1:1 ratio to either risankizumab (plus matching placebo for risankizumab) 150 mg SC at weeks 16, 20 (induction regimen), and 32, or continued treatment with adalimumab 40 mg (plus matching placebo for risankizumab) SC every other week through week 41.

All patients randomized to risankizumab in Part A continued risankizumab (150 mg SC every 12 weeks) plus matching placebo for adalimumab through week 44.

Outcomes

A detailed discussion of the validity of outcomes measures described in this section is provided in Appendix 5.

HRQoL was measured using the DLQI in each of the four trials. DLQI is a widely used dermatology-specific questionnaire to assess the impact of the disease on a patient's HRQoL. It consists of a 10-item patient-reported questionnaire assessing six different domains that may affect quality of life: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[18,40] The DLQI produces a numeric score that can range from 0 to 30; the higher the score, the greater the impairment in quality of life.[18,40]

DLQI scores are interpreted in the following way (estimates of minimal clinically important difference [MCID], range from 2.2 to 6.9):[18,19]

- 0 to 1 = no effect
- 6 to 10 = moderate effect
- 11 to 20 = very large effect
- 21 to 30 = extremely large effect

The following symptom-related efficacy end points were measured in all four trials:

- sPGA success: sPGA score of 0 indicating clear or 1 indicating almost clear
- PASI scores of 75, 90, or 100 (i.e., a 75%, 90%, or 100% improvement in the PASI score)

Psoriasis Area and Severity Index

The PASI is a widely used instrument in psoriasis trials and clinical practice that grades the severity of psoriatic lesions and the patient's response to treatment. It combines the extent of BSA involvement in four anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration or infiltration (thickness) in each region. In general, a PASI score from > 5 to 10 is considered moderate disease and a score above 10 is considered severe. A 75% reduction in the PASI score (PASI 75) was the traditional benchmark for clinical trials in psoriasis and was the criterion for the efficacy of new psoriasis treatments approved by the FDA.[41] However, according to a clinical expert consulted for this review, in current clinical practice the treatment goal is achievement of PASI 90 or PASI 100.

Static Physician Global Assessment

The sPGA is a single estimate of a physician's impression of patient's psoriasis. [42] In UltIMMA-1, UltIMMA-2, IMMvent, and IMMhance, sPGA was based on a composite score of a physician assessment of erythema, average thickness, and scaling of all psoriatic lesions. Each category was scored on a five-point scale (0 to 4); higher scores indicate more severe condition. The composite score falls on a scale of 0 to 4, interpreted as below:

- 0 = Cleared, except for residual discoloration
- 1 = Minimal
- 2 = Mild
- 3 = Moderate
- 4 = Marked
- 5 = Severe

No MCID for patients with plaque psoriasis was identified.

Psoriasis Symptoms Scale

The PSS is a patient-reported instrument that assesses the severity of psoriasis symptoms. Pain, redness, itching, and burning are rated by patients on a five-point Likert scale, from 0 (none) to four (very severe). In UltIMMA-1 and UltIMMA-2, the PSS was self-administered by patients using a daily diary from visits 2 to 6 and completed during clinics from visit 7 onward. Patients were asked to rate the severity of their symptoms over the past 24 hours using the following questions:

- How severe was your pain from your psoriasis during the past 24 hours?
- How severe was the redness from your psoriasis during the past 24 hours?
- How severe was your itching from your psoriasis during the past 24 hours?

- How severe was your burning from your psoriasis during the past 24 hours?
  - None
  - Mild
  - Moderate
  - Severe
  - Very severe

Although the PSS is based on two similar instruments, the Psoriasis Symptom Inventory and the Psoriasis Symptom Diary, which are validated instruments, no evidence of validity and reliability was available for the PSS.

Safety outcomes, including treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), were collected based on established definitions using the primary Medical Dictionary for Regulatory Activities system organ classes and preferred terms.

Statistical Analysis

The statistical analysis plan was similar in each of the four trials. In general, between-group treatment comparisons for categorical variables (PASI, sPGA) were conducted with a Cochran–Mantel–Haenszel test with body weight (≤ 100 kg versus > 100 kg) and prior TNF antagonist exposure (0 versus 1) as strata for the analysis. In cases where stratum did not contain any participants in any cell, the zero count was replaced by 0.1 to prevent dividing by zero. For continuous variables, an analysis of covariance (ANCOVA) was conducted to compare between-group treatment effects with treatment group, baseline value, and the stratification factors of baseline weight (≤ 100 kg versus > 100 kg) and prior exposure to TNF antagonists (0 versus ≥ 1) in the model. All treatment effects were based on a two-sided significance level of 0.05.

UltIMMA-1 and UltIMMA-2

Both studies were powered based on achievement of the co-primary end points (PASI 90 and an sPGA of clear or almost clear at week 16). Sample sizes were calculated assuming the PASI 90 response rate at week 16 would be 65% for the risankizumab arm and 45% for the ustekinumab arm, while the rate of achievement of sPGA clear or almost clear at week 16 was assumed to be 85% in the risankizumab arm and 67.5% in the ustekinumab arm. The assumed response rates were based on the results of the phase I and phase II studies in the risankizumab clinical development program. The assumed response rate for PASI 90 and sPGA for the placebo group was 5% for both end points. The total sample size required was 500 participants (300 for the risankizumab arm, and 100 each for the ustekinumab and placebo arms). Based on the 3:1 randomization scheme employed in the study, 300 participants in the risankizumab arm and 100 in the ustekinumab arm would yield 94% and 95% power for the PASI 90 and sPGA, respectively.

Multiplicity was handled by conducting statistical testing for the primary and ranked secondary variables in hierarchical order. If statistically significant results ($P \leq 0.05$) were not achieved for any outcome in the higher rank, statistical testing for all subsequent outcomes was not conducted. PASI 90 at week 16 was the first co-primary end point and an sPGA of clear or almost clear at week 16 was the second co-primary end point. No adjustment for multiplicity was applied, as the co-primary end points in Part A were required to demonstrate statistical significance simultaneously. Secondary outcomes were testing in the following hierarchical order:

1. Proportion of patients who achieved sPGA clear at week 16 (risankizumab versus placebo)
2. Proportion of patients who achieved PASI 100 at week 16 (risankizumab versus placebo)
3. Proportion of patients who achieved DLQI 0 or 1 at week 16 (risankizumab versus placebo)
4. Proportion of patients who achieved PSS 0 at week 16 (risankizumab versus placebo)
5. Proportion of patients who achieved PASI 90 at week 16 (risankizumab versus ustekinumab)
6. Proportion of patients who achieved sPGA clear or almost clear at week 16 (risankizumab versus ustekinumab)
7. Proportion of patients who achieved PASI 100 at week 16 (risankizumab versus ustekinumab)
8. Proportion of patients who achieved sPGA clear at week 16 (risankizumab versus ustekinumab)
9. Proportion of patients who achieved PASI 90 at week 52 (risankizumab versus ustekinumab)
10. Proportion of patients who achieved PASI 100 at week 52 (risankizumab versus ustekinumab)
11. Proportion of patients who achieved sPGA clear at week 52 (risankizumab versus ustekinumab)
12. Proportion of patients who achieved PASI 75 at week 12 (risankizumab versus ustekinumab)
13. Proportion of patients who achieved sPGA clear or almost clear at week 12 (risankizumab versus ustekinumab)
14. Proportion of patients who achieved DLQI 0 or 1 at week 16 (risankizumab versus ustekinumab)
15. PSS total score (change from baseline) at week 16 (risankizumab versus placebo)
16. Statistically significant results were achieved for each of the preceding ranked end points.

For categorical variables, the nonresponder imputation (NRI) was the primary analysis to control for missing data. In the NRI, participants were categorized as nonresponders if they had a missing value at any visit, unless that participant was a responder at the visits preceding and subsequent to the visit for which data were missing. The last observation carried forward (LOCF) approach was conducted as sensitivity analyses. For continuous variables, the LOCF was the primary approach and NRI was the secondary approach. The

multiple imputation approach was used as a sensitivity analysis for ranked primary and secondary end points.

Subgroups identified in the CDR review protocol that were analyzed on the co-primary efficacy end points in each of the four trials included body weight and prior exposure to TNF antagonists (both of which comprised the stratified analysis), disease severity (including patients with a PASI score above or below the median of each study), sPGA (moderate and severe), and history of psoriasis therapy (including those with and without previous exposure to non-biologic systemic therapy and those with and without previous exposure to any biologic therapy).

IMMhance

The IMMhance study was powered based on achievement of the co-primary end points (PASI 90 and sPGA clear or almost clear) at week 16 (Part A), and on sPGA at week 52 for patients re-randomized at week 28 (Part B). For Part A, the assumed response rates for the risankizumab arm were 65% for PASI 90 at week 16, and at least 80% for sPGA clear or almost clear at week 16. The assumed response rate for the placebo group was 5% for both end points. The assumed response rates were based on the results of the phase I and II studies in the risankizumab clinical development program. The total sample size required was 500 participants. Based on the 4:1 randomization scheme employed in Part A, 400 participants in the risankizumab arm and 100 in the placebo arm would yield > 99% power for the co-primary end points. For Part B, loss of response was assumed in, at most, 10% of patients re-randomized to the risankizumab arm and approximately 25% of patients re-randomized to the placebo arm. To achieve 90% power for the between-group comparison in sPGA response rate at week 52, 102 participants were required in the risankizumab arm and 204 participants were required in the placebo arm based on the 2:1 randomization scheme employed in Part B.

In the primary efficacy analysis for Part A, PASI 90 at week 16 was the first co-primary end point and an sPGA of clear or almost clear at week 16 was the second co-primary end point. No adjustment for multiplicity was applied, as the co-primary end points were required to demonstrate statistical significance simultaneously. The key efficacy end point in Part B, sPGA clear or almost clear at week 52 for re-randomized patients (patients randomized to risankizumab in Part A and re-randomized to risankizumab or placebo in Part B [ITT_B_R population]), was tested independently with a type I error rate of 0.05.

Multiplicity was handled by conducting statistical testing for the primary and ranked secondary variables in hierarchical order, as previously described for UltIMMA-1 and UltIMMA-2. Secondary outcomes for risankizumab versus placebo were testing in the following hierarchical order:

1. Proportion of patients who achieved PASI 75 at week 16
2. Proportion of patients who achieved PASI 100 at week 16
3. Proportion of patients who achieved sPGA clear at week 16
4. Proportion of patients who achieved DLQI 0 or 1 at week 16

Statistically significant results were achieved for each of the aforementioned ranked end points.

In Part B, the ranked secondary end point was the achievement of sPGA clear or almost clear (0 or 1) at week 104; this is not discussed in this review, as IMMhance is currently ongoing. All other secondary end points for Part B were not controlled for multiplicity.

Methods for imputing missing data and subgroups analyses in IMMhance were identical to those previously described for UltIMMA-1 and UltIMMA-2.

IMMvent

The IMMvent study was powered based on achievement of the co-primary end points (PASI 90 and sPGA clear or almost clear) at week 16 (Part A), and on PASI 90 at week 44 for patients re-randomized at week 16 in Part B. For Part A, the assumed response rates for the risankizumab arm were 65% for PASI 90 at week 16 and at least 85% for sPGA clear or almost clear at week 16. The assumed response rates were based on the results of the phase I and II studies in the risankizumab clinical development program. A sample size of 300 participants for each arm would yield > 90% power for both primary end points, assuming a response rate of 70% in the risankizumab arm and a 50% response rate in the adalimumab arm for PASI 90, and an achievement rate of 85% in the risankizumab arm and 70% in the adalimumab arm for sPGA clear or almost clear. For Part B, PASI 90 at week 44 was assumed to be approximately 40% for patients re-randomized to adalimumab and approximately 70% of patients re-randomized to risankizumab. The basis for these assumptions was not identified. To achieve 90% power for the between-group comparisons in PASI 90 at week 44 with a type I error rate of 0.05, a total of 120 participants were required. Approximately 40% of participants from Part A were expected to be eligible for re-randomization in Part B (i.e., be within PASI 50 and PASI 90 at week 16). Therefore, 300 patients were required in the adalimumab arm at randomization in Part A.

In the primary efficacy analysis for Part A, PASI 90 at week 16 was the first co-primary end point and sPGA clear or almost clear at week 16 was the second co-primary end point. No adjustment for multiplicity was applied, as the co-primary end points were required to demonstrate statistical significance compared with adalimumab simultaneously. The key efficacy end point in Part B, PASI 90 at week 44 for re-randomized patients (ITT_B_RR population), was tested independently; no adjustment for multiplicity was described. Each of these end points will be tested using a two-sided test with a type I error rate of 0.05.

Multiplicity was handled by conducting statistical testing for the ranked secondary variables in hierarchical order, as previously described for UltIMMA-1 and UltIMMA-2. Secondary outcomes were testing in the following hierarchical order:

1. Proportion of patients who achieved PASI 75 at week 16
2. Proportion of patients who achieved PASI 100 at week 16

Statistically significant results were achieved for each of the ranked end points in the preceding list.

The only ranked secondary end point for Part B was the achievement of PASI 100 at week 44 in the re-randomized patient population, which compared the results for the patients who continued adalimumab with those for the patients who switched to risankizumab. All other efficacy end points analyzed in Part B were outside of the statistical hierarchy and were not controlled for multiplicity.

Methods for imputing missing data and subgroups analyses in IMMvent were identical to those previously described for UltIMMA-1 and UltIMMA-2.

Analysis Populations

The main efficacy and safety analyses were conducted on the ITT and safety populations, respectively, in each of the four studies included in this CDR review. In all studies, the ITT population was defined as all patients who were randomized at baseline, and the patients included in all safety populations were required to have received at least one dose of the study drug and one post-baseline assessment. Specifically, in UltIMMA-1 and UltIMMA-2, the analysis populations were defined as follows:[20,21]

- ITT: All patients randomized at week 0. Patients who were randomized to the placebo arm in Part A did not continue into Part B of the study and were therefore excluded from the ITT population for Part B.
- Per-protocol: All patients who were compliant with the study protocol (those who received at least 75% of the study drug injections and who had either a PASI or sPGA assessment post-baseline and had stable moderate to severe plaque psoriasis at baseline).
- Safety: All randomized patients who received at least one dose of the study drug in Part A. Those who withdrew from the study prior to the start of Part B were not included in the safety analysis for Part B. The safety population for parts A and B included only patients who were randomized to either risankizumab or ustekinumab in Part A.
- All risankizumab: All patients who received at least one dose of risankizumab during the study.

In IMMhance and IMMvent, different ITT and safety populations were analyzed for different parts of the study. The populations, definitions, and notations for treatment groups discussed within the CDR review are summarized in Table 8 and Table 9.

Table 8: Analysis Populations in IMMhance

Population	Treatment Code	Definition	Objective
ITT_A1/Safety_A1	RZB	All patients randomized to risankizumab in Part A	To assess efficacy of initial treatment
	PBO	All patients randomized to placebo in Part A	
ITT_B_R/Safety_B_R	RZB/RZB/RZB	Patients randomized to risankizumab (arm 1) in Part A and re-randomized to risankizumab in Part B	To compare the efficacy of continued treatment with risankizumab versus withdrawal from the treatment. The risankizumab arm will also be summarized (including data after re-treatment) for long-term efficacy with the option of re-load
	RZB/RZB/PBO	Patients randomized to risankizumab (arm 1) in Part A and re-randomized to placebo in Part B	
ITT_B_NR/Safety_B_NR	RZB/RZB/RZB	Patients randomized to risankizumab in Part A and were nonresponders at week 28	To assess the potential delayed response
ITT_B_PBO_RT/ Safety_B_PBO_RT	RZB/RZB/PBO/RZB	Patients randomized to risankizumab in Part A and re-randomized to placebo in Part B and received at least one dose of re-treatment with open-label risankizumab after relapse	To assess response after re-treatment with risankizumab in patients who experienced relapse subsequent to drug withdrawal

Population	Treatment Code	Definition	Objective
ALL_RZB	RZB	Patients who received at least one dose of risankizumab during the study	To perform the safety analysis

ITT = intention-to-treat; PBO = placebo; RZB = risankizumab.

Note: ITT_B_RZB_RT included patients who received open-label risankizumab as re-treatment in Part B. However, as there are only three patients in this analysis population, no conclusions can be drawn; thus, the data for this population are not presented in this report.

Source: IMMhance Clinical Study Report.[22]

Table 9: Analysis Populations in IMMvent

Population	Treatment Code	Definition
ITT_A/Safety_A	ADA	All patients randomized to adalimumab in Part A
	RZB	All patients randomized to risankizumab in Part A
ITT_B_RR/Safety_B_RR	ADA/ADA	Patients randomized to adalimumab in Part A and re-randomized to adalimumab in Part B
	ADA/RZB	Patients randomized to adalimumab in Part A and re-randomized to risankizumab in Part B
Safety_B_R	ADA/ADA	Patients randomized to adalimumab at baseline and achieved PASI 90 at week 16 and received at least one dose of active adalimumab in Part B
ITT_B_NR/Safety_B_NR	ADA/RZB	Patients randomized to adalimumab in Part A and were nonresponders (failed to achieve PASI 50) at the entry of Part B who received at least one dose of risankizumab in Part B
ITT_B_RZB/ Safety_B_RZB	RZB/RZB	Patients randomized to risankizumab in Part A and who continued to receive risankizumab in Part B
ALL_RZB	RZB	Patients who received at least one dose of risankizumab during the study

ADA = adalimumab; ITT = intention-to-treat; PASI = PASI = Psoriasis Area and Severity Index; RZB = risankizumab.

Source: IMMvent Clinical Study Report.[23]

Analysis populations were stratified by body weight (≤ 100 kg versus > 100 kg) and previous treatment with TNF antagonists (0 versus ≥ 1) at randomization.

Patient Disposition

Patient dispositions for Part A and Part B of each study are presented in Table 10 and Table 11, respectively.

Overall, the majority of patients completed parts A and B of each study. In UltIMMA-1 and UltIMMA-2, 98% of patients completed Part A and more than 95% of patients completed Part B. Less than 1% of those patients who completed Part A did not receive any study drug in Part B in either study. In IMMhance, 98.6% of patients completed Part A1 and less than 1% of those did not continue the study. Part B of the IMMhance study is ongoing, with 4.2% of patients withdrawing from the study as of the interim analysis available for this review (September 1, 2017 cut-off date). In IMMvent, 96.7% of patients completed Part A and all of these patients entered Part B. The completion rate for Part B of IMMvent was high regardless of treatment group: 97.2% in patients continuing on adalimumab, 89.5% in patients switched from adalimumab to risankizumab (nonresponders), and 93.6% in re-randomized patients.

In general, the rate of withdrawals in Part A was higher in the placebo and adalimumab arms than in the risankizumab arm of each trial. Reasons for study withdrawal varied within and across trials. In Part B, the rate of withdrawals was generally low and similar across trials and well balanced within trials, with the exceptions of a higher rate of withdrawal in the ustekinumab/ustekinumab group in UltIMMA-1 and the adalimumab/adalimumab group in IMMvent. Similar to what was observed in Part A, reasons for study withdrawal varied within and across trials.

Table 10: Patient Disposition, Part A

	UltIMMA-1			UltIMMA-2			IMMhance[a]		IMMvent	
	PBO	UST	RZB	PBO	UST	RZB	PBO	RZB	ADA	RZB
Screened, N	560			577			563		684	
Randomized, N	102	100	304	98	99	294	100	407	304	301
Completed Part A, N (%)	98 (96.1)	99 (99.0)	299 (98.4)	94 (95.9)	96 (97.0)	292 (99.3)	97 (97.0)	403 (99.0)	291 (95.7)	291 (95.7)
Withdrawals, N (%)	4 (3.9)	1 (1.0)	5 (1.6)	4 (4.1)	3 (3.0)	2 (0.7)	3 (3.0)	4 (1.0)	[redacted]	[redacted]
AE	2 (2.0)	0	1 (0.3)	1 (1.0)	0	0	1 (1.0)	1 (0.2)	[redacted]	[redacted]
Protocol violation	0	0	0	0	0	0	0	0	[redacted]	[redacted]
Lost to follow-up	1 (1.0)	1 (1.0)	0	0	2 (2.0)	2 (0.7)	1 (1.0)	2 (0.5)	[redacted]	[redacted]
Patient withdrawal	1 (1.0)	0	3 (1.0)	3 (3.1)	0	0	1 (1.0)	1 (0.2)	[redacted]	[redacted]
Other	0	0	1 (0.3)	0	1 (1.0)	0	0	0	[redacted]	[redacted]
ITT, N	102	100	304	98	99	294	[redacted]	[redacted]	[redacted]	[redacted]
PP, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; AE = adverse event; ITT = intention-to-treat; PBO = placebo; PP = per-protocol; RZB = risankizumab; UST = ustekinumab.

[a] Patient disposition is for Part A1 (weeks 0 to 16).

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Table 11: Patient Disposition, Part B

	UltIMMA-1			UltIMMA-2			IMMhance[a]		IMMvent[b]	
	PBO/ RZB	UST/ UST	RZB/ RZB	PBO/ RZB	UST/ UST	RZB/ RZB	RZB/ RZB/ PBO	RZB/ RZB/ RZB	ADA/ ADA	ADA/ RZB
Dosed/re-randomized, N (%)	97 (100)	99 (99.0)	297 (97.7)	94 (100)	94 (94.9)	291 (99.0)	[redacted]	[redacted]	[redacted]	[redacted]
Completed Part B, N (%)	95 (97.9)	94 (94.0)	289 (95.1)	91 (96.8)	90 (90.9)	278 (94.6)	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawals, N (%)	2 (2.1)	5 (5.0)	8 (2.6)	3 (3.2)	4 (4.0)	13 (4.4)	[redacted]	[redacted]	[redacted]	[redacted]
AE	0	2 (2.0)	1 (0.3)	1 (1.1)	1 (1.0)	1 (0.3)	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	0	0	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	1 (1.0)	2 (2.0)	5 (1.6)	1 (1.1)	1 (1.0)	7 (2.4)	[redacted]	[redacted]	[redacted]	[redacted]
Patient withdrawal	1 (1.0)	1 (1.0)	2 (0.7)	0	2 (2.0)	4 (1.4)	[redacted]	[redacted]	[redacted]	[redacted]
Other	0	0	0	1 (1.1)	0	1 (0.3)	[redacted]	[redacted]	[redacted]	[redacted]
ITT, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	UltIMMA-1			UltIMMA-2			IMMhance[a]		IMMvent[b]	
	PBO/ RZB	UST/ UST	RZB/ RZB	PBO/ RZB	UST/ UST	RZB/ RZB	RZB/ RZB/ PBO	RZB/ RZB/ RZB	ADA/ ADA	ADA/ RZB
PP, N	[redacted]									
Safety, N	[redacted]									

ADA = adalimumab; AE = adverse event; ITT = intention-to-treat; PBO = placebo; PP = per-protocol; RZB = risankizumab; UST = ustekinumab.

[a] Patient disposition is for the ITT_B_R population: patients who were randomized to risankizumab in Part A (arm 1) and re-randomized at week 28. Patient disposition for Part B is based on the interim analysis (data cut-off date was September 1, 2017).

[b] Patient disposition is for the ITT_B_RR population: patients who were randomized to adalimumab at baseline and re-randomized at week 16.

[c] Number of patients ongoing in Part B.

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Exposure to Study Treatments

Mean adherence was > 97% in UltIMMA-1, > 98% in UltIMMA-2, > 99% in IMMhance, and > 96% in IMMvent for all groups throughout the duration of each study (note that, as IMMhance is ongoing, the data reflects adherence only up to week 52). Adherence was comparable and generally well balanced between treatment arms throughout parts A and B of each study.

Exposure to the study drug for parts A and B of each study is summarized in Table 12. In UltIMMA-1 and UltIMMA-2, exposure to study treatment was comparable between groups throughout the study. In IMMhance, study-drug exposure was similar between treatment groups in Part A, but was higher in patients re-randomized to risankizumab versus placebo in Part B. In IMMvent, study-drug exposure was similar between treatment groups in Part A, but was higher in patients re-randomized to adalimumab in Part B.

Table 12: Extent of Exposure to Study Treatment

	UltIMMA-1[a]			UltIMMA-2[a]			IMMhance[b]		IMMvent[c]	
Part A	**PBO**	**UST**	**RZB**	**PBO**	**UST**	**RZB**	**PBO**	**RZB**	**ADA**	**RZB**
Analysis-set patients treated, n	[redacted]									
Mean adherence										
Mean number of injections										
Days of exposure to study drug, mean (SD)										
Part B	**PBO/ RZB**	**UST/ UST**	**RZB/ RZB**	**PBO/ RZB**	**UST/ UST**	**RZB/ RZB**	**RZB/RZB/ PBO**	**RZB/RZB/RZB**	**ADA/ ADA**	**ADA/ RZB**
Analysis-set patients treated, n	[redacted]									
Mean adherence										
Mean number of injections										
Days of exposure to study drug, mean										

	UltIMMA-1[a]			UltIMMA-2[a]			IMMhance[b]		IMMvent[c]	
(SD)										

ADA = adalimumab; PBO = placebo; RZB = risankizumab; SD = standard deviation; UST = ustekinumab.

[a] For patients who did not continue into Part B: Duration = Last injection date in Part A minus first injection date in Part A plus 84. For patients who continued into Part B: Duration = The minimum of first injection date in Part B minus first injection date in Part A **and** last injection date in Part A minus first injection date in Part A plus 84.

[b] For patients who did not continue into Part A2: Duration = Date of last injection in Part A1 minus date of first injection in Part A1 plus 84. For patients who continued into Part A2: Duration = The minimum of the date of first injection in Part A2 minus date of first injection in Part A1 **and** the date of last injection in Part A1 minus the date of first injection in Part A1 plus 84 days.

[c] For ADA:
For patients who did not continue into Part B: Duration = Last injection date in Part A minus first injection date in Part A plus 14.
For patients who continued into Part B: Duration = The minimum of first injection date in Part B minus first injection date in Part A **and** last injection date in Part A minus first injection date in Part A plus 14.

For RZB:
For patients who did not continue into Part B: Duration = Last injection date in Part A minus first injection date in Part A plus 84.
For patients who continued into Part B: Duration = The minimum of first injection date in Part B minus first injection date in Part A **and** last injection date in Part A minus first injection date in Part A plus 84.
For ADA/ADA: Duration = The last injection date in Part B minus first injection date in Part B plus 14.
For ADA/RZB: Duration = The last injection date in Part B minus first injection date in Part B plus 84.

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Critical Appraisal

Internal Validity

Study Design and Methodology

Overall, the included trials generally appear to have been performed with methodological rigour, including in terms of the preservation of blinding, concealment of treatment allocation, use of validated instruments to measure outcomes, and use of an appropriate statistical analysis plan (including appropriate adjustments for multiplicity of co-primary and ranked secondary end points and appropriate imputation for missing data); therefore, risk of bias was low during both Part A and Part B of each study. In each of the trials, patients were required to stop previous treatment for a pre-specified duration depending on the treatment, thereby minimizing potential carry-over effects from previous psoriasis treatments. However, in each of the four trials, sample size was not calculated with consideration of the subgroups analyses, which may lack statistical power; therefore, the results of these analyses should be interpreted with consideration for type II error.

It is unlikely that the internal validity of the key efficacy end point for Part B was significantly compromised as a result of the re-randomization of patients who satisfied a pre-specified criteria. Re-randomization of a pre-specified patient population is considered a strength of an adaptive trial design.

In order to maintain double-blinding during treatment, double-dummy placebos were administered. There was no obvious indication of unblinding in the trials; however, in IMMhance, open-label treatment with risankizumab was administered to patients who did not respond to risankizumab or placebo treatment during Part A or who experienced relapse in Part B. Open-label treatment with risankizumab may have biased the results in these analysis populations, since PASI response, sPGA, and DLQI are subjective measures. Patients switching from placebo during Part A to risankizumab during Part B did not receive the induction regimen in UltIMMA-1 and UltIMMA-2; therefore, the validity of findings from this group of patients is questionable. In the IMMvent trial, some adalimumab nonresponders were re-randomized to risankizumab, while others were re-randomized to

continued treatment with adalimumab. Treating nonresponders with a drug to which they have previously demonstrated an inadequate response could bias results in favour of risankizumab. Adalimumab nonresponders who experienced a response after being re-randomized (as compared with nonresponders who continued on the drug they were not responding to) may have become alerted to the switch. As a result, it is possible that patients or physicians may have inferred the treatment group to which they or their patient had been randomized and, thus, blinding may have been sacrificed in Part B of the IMMvent study in the re-randomized population.

Adherence was generally high throughout each study and well balanced across treatment groups; it was therefore unlikely to create bias in favour of any treatment.

Baseline Characteristics and Patient Disposition

Imbalances in patient population were identified for a number of baseline disease characteristics, namely, PASI score at baseline in UltIMMA-2, and previous treatment exposure varied widely across studies. Specifically, the proportion of patients previously treated with a biologic was imbalanced across treatment groups in UltIMMA-1, which may have introduced bias in the treatment effect in favour of both the ustekinumab and risankizumab groups. The number of patients with previous biologic experience within each treatment group is relatively small, so the potential impact on the treatment effect may not be substantial; however, the magnitude of this potential effect remains unknown. In addition, mean body weight in UltIMMA-1 was lower than in the other three studies included in this review. While there is potential that these imbalances introduced confounding factors, the magnitude of the treatment difference in each study is large and highly significant. Further, results are consistent across the four trials. Therefore, it is expected that the impact of these imbalances is minimal.

The proportion of patients who discontinued the study was low and well balanced across treatment groups in parts A and B of each study included in this review. The main reasons for study withdrawal included adverse events (AEs), protocol violation, lost to follow-up, and patient withdrawal. There was no clear trend in any of these reasons for withdrawal in any of the treatment groups across any of the studies. Therefore, it is unlikely that the withdrawal rate or reason would compromise randomization or bias the estimation of the treatment effect.

Statistical Analysis

Efficacy analyses were based on the ITT population. In UltIMMA-1 and UltIMMA-2, the anticipated treatment effects of PASI 90 and sPGA clear or almost clear were assumed for the power calculations and were based on previous trials of risankizumab. The assumed magnitude of the treatment difference was approximately 15% to 20% in each of the trials and was confirmed to be clinically relevant by the clinical expert consulted for this CDR review.

The UltIMMA-1 and UltIMMA-2 studies were powered based on achievement of the co-primary end points (PASI 90 and an sPGA of clear or almost clear at week 16). In IMMhance and IMMvent, power and sample size were calculated based on co-primary end points in Part A and the key efficacy end point for the re-randomized patient population in Part B. The rate of withdrawal was low across all trials and treatment groups; thus, it is unlikely that power was affected. Therefore, sample size should be considered adequate for all statistical comparisons in parts A and B of each of the studies.

The included trials had sufficient power to test the significance of the co-primary outcomes in Part A. IMMhance and IMMvent were also powered to test the significance of a key efficacy outcome in Part B, which was tested independently as per the statistical analysis plan for each study. However, treatment allocation in Part B was dependent on the results of Part A; therefore, the trial design is not completely independent. No multiplicity adjustments were made for the key efficacy end point in Part B; however, type I error is an unlikely explanation of the statistically significant findings at the end of Part B (52 weeks for the IMMhance interim analysis and 44 weeks for IMMvent), given the magnitude of the observed treatment effect and small *P* value. Secondary outcomes were tested only if the co-primary end points were achieved simultaneously. A ranked hierarchy was employed for statistical analysis of secondary outcomes, which is an appropriate control for multiplicity. However, outcomes that fall outside of the statistical testing hierarchy (e.g., PASI 75 at week 16 in UltIMMA-1 and UltIMMA-2, DLQI for Part B) were not controlled for multiplicity and should be interpreted with consideration of the risk of type I error.

All analyses for primary and secondary outcomes were conducted in the ITT population. Sensitivity analyses were conducted using data from the per-protocol populations to support the primary findings, and the results were consistent with the primary analysis (data not shown). Missing data for categorical variables were imputed using the NRI approach as the primary analysis, which is the standard approach for handling missing data. Given that no meaningful differences between treatment groups with respect to withdrawal rate or reason for withdrawal were observed within any of the trials, missingness is not likely to impact the interpretation of the results.

Outcome Measures

The outcome measures and definitions used in all four trials, including the sPGA and PASI response, have evidence of validity in psoriasis and are considered appropriate to evaluate treatment response in psoriasis clinical trials. Although the sPGA is considered to have good test–retest reliability and internal consistency, inter-rater reliability is poor, which is also a key limitation of the PASI response. An MCID has not been identified for either the sPGA or PASI response; however, the current benchmark for clinical trials is a 90% to 100% reduction in PASI score (i.e., PASI 90 or PASI 100), both of which were measured in the four clinical trials in this review. The clinical expert acknowledged that while measurement of PASI 90 is clinically meaningful, for patients, the incremental relevance of responses above PASI 75 is unknown and of uncertain clinically significant value.

The DLQI is also frequently used to capture the different aspects of patients' lives that are affected. The DLQI is considered valid and reliable, with an estimated MCID in the range of 2.2 to 6.9.[18,19] The DLQI has shown good test–retest reliability based on a reassessment seven to 10 days after the initial assessment (the correlation between overall DLQI scores was 0.99; $P < 0.0001$; for individual question scores, the correlation was 0.95 to 0.98; $P < 0.001$).[40] The DLQI has also shown good internal consistency reliability (with Cronbach's alpha coefficients ranging from 0.75 to 0.92).[19] There is no evidence to support the validity or reliability of the PSS.

External Validity

Generalizability of the Study Population

The inclusion and exclusion criteria were similar across the four trials included in this review. All patients included in all of the trials had stable moderate to severe plaque psoriasis, which was reflected in the baseline demographic characteristics of each study and is aligned with the target patient population in the Health Canada indication for risankizumab. The inclusion criteria (BSA involvement of ≥ 10%, PASI ≥ 12, and sPGA ≥ 3) accurately reflect the patient population with moderate to severe psoriasis, as defined by the Canadian Guidelines for the Management of Plaque Psoriasis.[6] Most cases were moderate in severity. The clinical expert consulted for this review noted that determination of disease severity in clinical practice often varies across physicians and is determined in part by the patient's perception of their disease; thus, there is potential for risankizumab (as with other biologics) to be used in patients with less severe (i.e., mild) or localized cases of psoriasis. Treatment effects of risankizumab observed across the four trials may not be generalizable to patients with mild plaque psoriasis; however, this is beyond the indication for risankizumab approved by Health Canada. According to the clinical expert consulted on this review, the baseline characteristics of the study populations reflect a patient population with moderate to severe plaque psoriasis that is consistent with what would be seen in Canadian clinical practice.

Various groups of patients with comorbid conditions were excluded from the trials, including patients with current or a history of malignant disease or chronic or relevant acute infections such as active or latent tuberculosis, HIV, or hepatitis C or hepatitis B, which is consistent with other clinical trials for drugs to treat psoriasis. From a clinical perspective, such exclusion criteria are not unreasonable, given the immunomodulating effects of these drugs and their potential impact on these patient subpopulations, who may be at an increased risk for developing infections and malignancies. Therefore, the findings from these trials may not be generalizable to patients with these conditions. In addition, all patients who had ever received risankizumab, ustekinumab, or adalimumab were also excluded from UltIMMA-1 and UltIMMA-2, and IMMvent, respectively, so results may not be generalizable to patients who have previous experience and whose disease is refractory to treatment with multiple biologic drugs. The IMMvent trial supports the efficacy of risankizumab in patients who did not exhibit a response to treatment with adalimumab; however, whether a similar effect would be observed following treatment with other biologics is unknown.

Finally, all trials included study sites in Canada and thus included Canadian patients with moderate to severe plaque psoriasis.

Previous exposure to traditional systemic treatment ranged from 37% to 58% in the trials included in this review, which was noted by the clinical expert consulted for this review to be substantially lower than the rate of exposure observed in Canada. Based on input from the clinical expert consulted for this review, in Canada, the majority of patients starting biologic treatment would have previously tried traditional systemic treatment. Further, patients were not permitted to use any traditional systemic treatments, photochemotherapy, phototherapy, or any topical treatments throughout the duration of the study. Therefore, results of the clinical trials of risankizumab are not generalizable to patients using other treatments in addition to biologics.

Intervention and Comparators

The comparators used in the clinical trials (ustekinumab in UltIMMA-1 and UltIMMA-2, adalimumab in IMMvent) were appropriate comparators and were the forerunners of biologic treatment at the time the studies were initiated, according to the clinical expert consulted for this CDR review. The treatment regimens for ustekinumab and adalimumab followed in the clinical trials are as per the Health Canada–recommended dosing for each drug. However, there is no direct evidence to demonstrate the comparative efficacy and safety of risankizumab with IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) or the IL-23 inhibitor guselkumab which, according to the clinical expert consulted for this CDR review, have replaced the TNF-alpha inhibitors as the most commonly used biologic treatments in Canada. Two indirect treatment comparisons (ITCs) were identified for inclusion in this CDR review to address this evidence gap; these ITCs are reviewed and critically appraised in Appendix 7.

In general, the dosage regimen for risankizumab administered in each of the trials included in the CDR review follows the dosing recommended by Health Canada. The exception is the patients who were randomized to placebo at baseline and switched to risankizumab for Part B in UltIMMA-1 and UltIMMA-2. No induction regimen of risankizumab was administered to that group; instead, patients received risankizumab once every 12 weeks throughout Part B of the studies. Results from those arms of the trials are thus not generalizable to the Canadian patient population, as this administration schedule is not reflective of Canadian clinical practice.

In IMMvent, the key objective of Part B was to assess the efficacy and safety of switching from adalimumab to risankizumab. This objective was investigated in patients who had an inadequate response to adalimumab based on PASI response and were re-randomized to continue treatment with adalimumab or were switched to risankizumab (ITT_B_RR population). Patients who were switched to risankizumab did not undergo a washout period, which is representative of clinical practice. However, according to the clinical expert consulted for the CDR review, prior to switching to another biologic, it is common practice to increase the dose of the current biologic treatment in patients who have an inadequate response prior to switching to another biologic. In IMMvent, the dose of adalimumab was not adjusted prior to switching patients identified as nonresponders to risankizumab. Therefore, the switching protocol employed in these studies does not appear to be reflective of clinical practice in Canada and it remains uncertain whether the results obtained from this subset of patients are generalizable to Canada. Current Canadian psoriasis guidelines do not mention increasing the dose of adalimumab in patients who do not respond to the drug.[5]

Results of Part A from each of the trials, where only the induction regimen of risankizumab was administered, could be of particular interest to Canadian physicians. Based on input from the clinical expert consulted from this review, a 16-week period is adequate to determine patient response; however, given that psoriasis is a chronic condition requiring lifelong treatment, the 52-week trial duration is insufficient to determine whether risankizumab will be efficacious and safe over the long term.

Outcome Measures

The primary and secondary outcome measures and definitions in the four trials included in this review (i.e., DLQI, PASI response, sPGA) are well-accepted measures to evaluate treatment response in clinical trials of therapeutic interventions for psoriasis and are

considered valid and reliable, as described in Appendix 5. As corroborated by the clinical expert consulted for this review, the outcomes measured in the trials are clinically relevant measures of treatment effect. However, the clinical expert also noted that these measures are highly subjective and are not typically used to measure disease severity or treatment response in clinical practice. PASI 90 was a co-primary outcome in all four of the trials, which is relevant according to the clinical expert consulted for this review, as it represents the current standard goal for skin clearance.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported subsequently. See Table 13, Table 14, and Table 15 for detailed efficacy data.

Health-Related Quality of Life

Dermatology Life Quality Index

Part A

As shown in Table 13, a statistically significantly larger proportion of patients achieved a DLQI score of 0 or 1 at week 16 in the risankizumab group compared with: the placebo and ustekinumab groups in UltIMMA-1 (65.8% versus 7.8%, adjusted difference: 57.9; 95% CI, 50.4 to 65.3; and 43.0%, adjusted difference: 23.0; 95% CI, 11.9 to 34.0; $P < 0.001$ for both) and UltIMMA-2 (66.7% versus 4.1%, adjusted difference: 62.2; 95% CI, 55.5 to 68.9; and 46.5%, adjusted difference: 20.2; 95% CI, 9.1 to 31.4; $P < 0.001$ for both); and the placebo group in IMMhance (65.4% versus 3.0%, adjusted difference: 62.1; 95% CI, 56.4 to 67.9; $P < 0.001$). A DLQI score of 0 or 1 at week 16 was a ranked secondary end point in these three trials, and results were controlled for multiplicity. In IMMvent, more patients in the risankizumab group achieved a DLQI score of 0 at week 16 than in the adalimumab group (65.8% versus 48.7%, adjusted difference: 17.1; 95% CI, 9.3 to 24.8), but this outcome was not included as a ranked secondary end point.

Mean change (standard error [SE]) from baseline in DLQI at week 16 was [redacted]); and adalimumab (−11.5 [0.30] versus −9.7 [0.29], least squares mean treatment difference: [redacted]; $P < 0.001$). Change from baseline in DLQI was not a ranked secondary end point in any of the studies included in this review.

Part B

The score on the DLQI and the DLQI change from baseline in Part B were not included in the statistical hierarchy for any of the trials included in this CDR review; therefore, results summarized in this section must be interpreted with consideration of type I error. Data were not provided summarizing achievement of a DLQI score 0 or 1 or DLQI change from baseline in Part B of the IMMhance study.

In UltIMMA-1, the proportion of patients who achieved a DLQI score of 0 or 1 at week 52 [redacted] The proportion of patients who achieved a DLQI score of 0 or 1 at week 52 was [redacted] in patients randomized to placebo in Part A and switched to risankizumab in Part B.

In UltIMMA-2, the proportion of patients who achieved a DLQI score of 0 or 1 was [redacted]). The proportion of patients who achieved a DLQI score of 0 or 1 at week 52 was [redacted] in patients randomized to placebo in Part A and switched to risankizumab in Part B.

In IMMvent, in the ITT_B_RR population, the proportion of patients who achieved a DLQI score of 0 or 1 at week 44 was 39.6% of the patients re-randomized to risankizumab and 39.3% of the patients re-randomized to adalimumab (adjusted difference: [redacted]).

In UltIMMA-1, mean (SE) change from baseline in DLQI at week 52 was [redacted]). Mean change from baseline in DLQI at week 52 was [redacted] in patients randomized to placebo in Part A and switched to risankizumab in Part B.

Similar results were observed during UltIMMA-2, where mean (SE) change from baseline in DLQI at week 52 was [redacted]). Mean change from baseline in DLQI at week 52 was [redacted] in patients randomized to placebo in Part A and switched to risankizumab in Part B.

In IMMvent, mean change from baseline in DLQI at week 44 was [redacted]). The proportion of patients achieving a DLQI score of 0 or 1 at week 44 in the [redacted]. Mean (SE) change in DLQI from baseline to week 44 was [redacted] population.

Skin Clearance

Psoriasis Area and Severity Index Response

Part A

PASI 90 at week 16 was a co-primary end point in each of the studies included in this review and was achieved in all four studies. A statistically significantly larger proportion of patients in the ITT population achieved PASI 90 at week 16 in the risankizumab group compared with: the placebo and ustekinumab groups in UltIMMA-1 (75.3% versus 4.9%, adjusted difference: 70.3; 95% CI, 64.0 to 76.7; and 42.0% adjusted difference: 33.5; 95% CI, 22.7 to 44.3; $P < 0.001$ for both) and UltIMMA-2 (74.8% versus 2.0%, adjusted difference:

72.5; 95% CI, 66.8 to 78.2; and 47.5%, adjusted difference: 27.6; 95% CI, 16.7 to 38.5; $P < 0.001$ for both); the placebo group in IMMhance (73.2% versus 2.0%, adjusted difference: [redacted]; $P < 0.001$); and the adalimumab group in IMMvent (72.4% versus 47.4%, adjusted difference: [redacted]; $P < 0.001$).

Statistically significant results were observed for PASI 100 at week 16, where a larger proportion of patients in the ITT population achieved PASI 100 at week 16 in the risankizumab group compared with: the placebo and ustekinumab groups in UltIMMA-1 (35.9% versus 0%, adjusted difference 35.5; 95% CI, 30.0 to 41.0; and 12.0%, adjusted difference: 23.8; 95% CI, 15.5 to 32.1; $P < 0.001$ for both) and UltIMMA-2 (50.7% versus 2.0%, adjusted difference: 48.2; 95% CI, 41.9 to 54.6; and 24.2%, adjusted difference: 27.0; 95% CI, 17.0 to 37.0; $P < 0.001$ for both); the placebo group in IMMhance (47.2% versus 1.0%, adjusted difference: 45.5; 95% CI, 40.3 to 50.8; $P < 0.001$); and the adalimumab group in IMMvent (39.9% versus 23.0%, adjusted difference: 16.7; 9.5 to 23.9; $P < 0.001$).

As would be expected based on results for the proportion of patients who achieved PASI 90 and PASI 100 at week 16, a larger proportion of patients achieved PASI 75 at week 16 in the risankizumab group compared with: the placebo and ustekinumab groups in UltIMMA-1 (89.1% versus 8.8%, adjusted difference: 80.2; 95% CI, 73.8 to 86.7; $P < 0.001$; and 76.0%, adjusted difference: 13.3; 95% CI, 4.4 to 22.3; $P = 0.003$) and UltIMMA-2 (90.8% versus 6.1%, adjusted difference: 84.7; 95% CI, 79.0 to 90.4; and 69.7%, adjusted difference: 21.2; 95% CI, 11.7 to 30.7; $P < 0.001$ for both); the placebo group in IMMhance (88.7% versus 8.0%, adjusted difference: 80.6; 95% CI, 74.5 to 86.6; $P < 0.001$); and the adalimumab group in IMMvent (90.7% versus 71.7%, adjusted difference: 18.9; 95% CI, 13.0 to 24.9; $P < 0.001$). PASI 75 at week 16 was a ranked secondary end point in IMMhance and IMMvent; however, it was outside the hierarchical testing procedure in UltIMMA-1 and UltIMMA-2 and statistical analyses were not controlled for multiplicity in these trials. Detailed results for PASI 75 at week 16 are shown in Table 22.

Subgroups of Interest

A stratified analysis by body weight (≤ 100 kg versus > 100 kg) and previous treatment with TNF antagonists (0 versus ≥ 1) was conducted on the co-primary end points. Results of the stratified analysis are shown in Table 23.

In the stratified analysis, the proportion of patients that achieved PASI 90 at week 16 was statistically significantly greater in the risankizumab group compared with placebo across all strata in UltIMMA-1, UltIMMA-2, and IMMhance (Table 23).

Results of subgroup analysis were generally similar to those observed in the full ITT population in each of the four trials in that risankizumab was superior to ustekinumab or adalimumab in terms of PASI 90. However, PASI 90 was not statistically significantly different for risankizumab versus ustekinumab in patients with baseline weight > 100 kg and with prior exposure to TNF antagonists (68.2% versus 40.0%, difference: 28.2; 95% CI, −19.0 to 75.3; $P = 0.326$) in UltIMMA-1 or in patients with baseline weight ≤ 100 kg and with prior exposure to TNF antagonists (70.7% versus 46.2%, difference: 24.6; 95% CI, −5.9 to 55.0; $P = 0.181$) in UltIMMA-2; and not statistically different from adalimumab in patients with baseline weight > 100 kg and no prior exposure to TNF antagonists (59.4% versus 47.8%, difference: 11.5; 95% CI, −5.3 to 28.4; $P < 0.182$) in IMMvent.

Additional subgroup analyses conducted on the co-primary end points in the trials and of relevance to this review included measures of disease severity and history of psoriasis therapy. Overall, treatment effects in each subgroup were consistent with the primary

analysis in that a greater proportion of patients in the risankizumab group achieved PASI 90 at week 16 compared with patients in the placebo group (Table 24). However, sample size was not calculated with consideration of these subgroups analyses, which may therefore lack statistical power and results of these analyses should be interpreted with consideration for type II error.

Part B

In Part B of UltIMMA-1 and UltIMMA-2, patients randomized to either risankizumab or ustekinumab continued their assigned treatment up to week 52, while patients originally randomized to placebo were switched to risankizumab. The proportion of patients who achieved PASI 90 at week 52 was statistically significantly greater in patients who continued treatment with risankizumab versus ustekinumab in UltIMMA-1 (81.9% versus 44.0%, adjusted difference: 38.3; 95% CI, 27.9 to 48.6; $P < 0.001$) and UltIMMA-2 (80.6% versus 50.5%, adjusted difference: 30.2; 95% CI, 19.6 to 40.9; $P < 0.001$). The proportion of patients who achieved PASI 90 in the group randomized to placebo in Part A and switched to risankizumab in Part B was 78.4% in UltIMMA-1 and 85.1% in UltIMMA-2; no statistical comparisons were conducted against this group. Similarly, the proportion of patients who achieved PASI 100 at week 52 was statistically significantly greater in patients who continued treatment with risankizumab versus ustekinumab in UltIMMA-1 (56.3% versus 21.0%, adjusted difference: 32.4; 95% CI, 22.0 to 42.9; $P < 0.001$) and UltIMMA-2 (59.5% versus 30.3%, adjusted difference: 29.5; 95% CI, 18.9 to 40.1; $P < 0.001$). The proportion of patients who achieved PASI 100 in the group randomized to placebo in Part A and switched to risankizumab in Part B was 54.6% in UltIMMA-1 and 67.0% in UltIMMA-2; no statistical comparisons were conducted against this group.

The objective of Part B in the IMMhance study was to compare the efficacy of continued treatment with risankizumab versus withdrawal from the treatment (ITT_B_R population). The proportion of patients who achieved PASI 90 at week 52 in the ITT_B_R population was 85.6% in patients who continued risankizumab versus 52.4% in patients who switched to placebo (adjusted difference: 33.1; 95% CI, 24.0 to 42; $P < 0.001$). As of week 32 in Part B, patients re-randomized to placebo who experienced relapse received open-label risankizumab 0, 4, and 16 weeks after relapse. PASI 90 at week 16 of re-treatment was achieved in 65.0% of the patients who were switched to placebo and experienced a relapse and were re-treated with open-label risankizumab. The proportion of patients who achieved PASI 100 at week 52 in the ITT_B_R population was 64.0% in patients who continued risankizumab versus 30.2% in patients who switched to placebo (adjusted difference: 33.7; 95% CI, 23.2 to 44.2; $P < 0.001$). PASI 100 at week 16 of re-treatment was achieved in 37.5% of the patients who were switched to placebo and experienced a relapse and were re-treated with open-label risankizumab. PASI 90 and PASI 100 at week 52 were not included in the hierarchical statistical testing procedure and were not controlled for multiplicity. A summary of these results is presented in Table 25.

The results of Part B for the ITT_B_RR population in the IMMvent study are shown in Table 15. In IMMvent, switching to risankizumab was superior to continuing on adalimumab in the re-randomized patient population (ITT_B_RR) in terms of achieving PASI 90; 66.0% of patients re-randomized to risankizumab versus 21.4% of those who continued on adalimumab achieved PASI 90 at week 44 (adjusted difference: 45.0; 95% CI, 28.9 to 61.1; $P < 0.001$), thus achieving the primary end point for Part B. This was the primary end point in Part B and was tested independently. This result was supported by the LOCF sensitivity and per-protocol analyses. As the primary end point was met, statistical testing was conducted for the ranked secondary end point of PASI 100 at week 44 in the ITT_B_RR

population. The proportion of patients who achieved PASI 100 at week 44 in patients re-randomized to risankizumab was 39.6% versus 7.1% of those who continued on adalimumab (adjusted difference: 32.8; 95% CI, 18.8 to 46.9; *P* < 0.001). This was a ranked secondary end point and thus controlled for multiplicity. The proportion of patients achieving PASI 90 and PASI 100 was also measured at week 44 in the ITT_B_R population (75.7% and 49.3%, respectively), ITT_B_NR (patients randomized to adalimumab in Part A and were non-responders (failed to achieve PASI 50) at the entry of Part B who received at least one dose of risankizumab in Part B)population (60.5% and 36.8%, respectively), and ITT_B_RZB (patients randomized to risankizumab in Part A and continued to receive risankizumab in Part B) population (75.7% and 52.8%, respectively); see Table 26 for a summary of results.

Static Physician Global Assessment

Part A

An sPGA of clear or almost clear at week 16 was a co-primary end point in each of the studies included in this review and was achieved in all four studies. A statistically significantly larger proportion of patients achieved sPGA clear or almost clear at week 16 in the risankizumab group compared with: the placebo and ustekinumab groups in UltIMMA-1 (87.8% versus 7.8%, adjusted difference: 79.9; 95% CI, 73.5 to 86.3, and 63.0%, adjusted difference: 25.1; 95% CI, 15.2 to 35.0; *P* < 0.001 for both) and UltIMMA-2 (83.7% versus 5.1%, adjusted difference: 78.5; 95% CI, 72.4 to 84.5, and 61.6%, adjusted difference: 22.3; 95% CI, 12.0 to 32.5; *P* < 0.001 for both); the placebo group in IMMhance (83.5% versus 7.0%, adjusted difference: 76.5; 95% CI, 70.4 to 82.5; *P* < 0.001); and the adalimumab group in IMMvent (83.7% versus 60%, adjusted difference: 23.3; 95% CI, 16.6 to 30.1; *P* < 0.001).

Similar results were observed for sPGA clear at week 16, where a statistically significantly larger proportion of patients achieved sPGA clear at week 16 in the risankizumab group compared with: the placebo and ustekinumab groups in UltIMMA-1 (36.8% versus 2.0%, adjusted difference: 34.7; 95% CI, 28.6 to 40.8; and 14.0%, adjusted difference: 22.9; 95% CI, 14.3 to 31.6; *P* < 0.001 for both) and UltIMMA-2 (51.0% versus 3.1%, adjusted difference: 47.5; 95% CI, 40.9 to 54.2, and 25.3%, adjusted difference: 26.3; 95% CI, 16.1 to 36.4; *P* < 0.001 for both); the placebo group in IMMhance (46.4% versus 1.0%, adjusted difference: 44.8; 95% CI, 39.5 to 50.0; *P* < 0.001); and the adalimumab group in IMMvent (41.2% versus 23.4%, adjusted difference: 17.7; 95% CI, 10.4 to 24.9; *P* < 0.001).

Subgroups of Interest

A stratified analysis by body weight (≤ 100 kg versus > 100 kg) and previous treatment with TNF antagonists (0 versus ≥ 1) was conducted on the co-primary end points. Results of the stratified analysis are shown in Table 23.

In the stratified analysis, the proportion of patients who achieved sPGA clear or almost clear at week 16 was statistically significantly greater in the risankizumab group compared with placebo across all strata in UltIMMA-1, UltIMMA-2, and IMMhance (Table 23).

Risankizumab was statistically significantly different from ustekinumab in terms of sPGA clear or almost clear at week 16 except in patients with baseline weight > 100 kg and no prior exposure to TNF antagonists (85.7% versus 71.4%, difference: 14.3; 95% CI, −7.1 to 35.7; *P* = 0.187), and in patients with baseline weight > 100 kg and with prior exposure to TNF antagonists (77.3% versus 60.0%, difference: 17.3; 95% CI, −29.1 to 63.6; *P* = 0.580),

in UltIMMA-1; in patients with baseline weight ≤ 100 kg and with prior exposure to TNF antagonists (82.9% versus 53.8%, difference: 29.1; 95% CI, −0.4 to 58.5; *P* = 0.059), or in patients with baseline weight > 100 kg and with prior exposure to TNF antagonists (84.6% versus 63.6%, difference: 21.0; 95% CI, −10.7 to 52.6; *P* = 0.203), in UltIMMA-2. In IMMvent, risankizumab was statistically significantly different from adalimumab in terms of sPGA clear or almost clear at week 16 except in patients with baseline weight > 100 kg and no prior exposure to TNF antagonists (67.2% versus 58.0%, difference: 9.2; 95% CI, −7.2 to 25.6; *P* = 0.273), or in patients with baseline weight ≤ 100 kg and with prior exposure to TNF antagonists (84.6% versus 70.4%, difference: 14.2; 95% CI, −7.9 to 36.4; *P* = 0.215).

Additional subgroup analyses conducted on the co-primary end points in the trials and of relevance to this review included measures of disease severity and history of psoriasis therapy. Overall, treatment effects in each subgroup were consistent with the primary analysis in that a greater proportion of patients in the risankizumab group achieved sPGA clear or almost clear at week 16 compared with patients in the placebo group (Table 24).

Part B

In Part B of UltIMMA-1 and UltIMMA-2, the proportion of patients who achieved sPGA clear or almost clear at week 52 was not a ranked secondary end point and not controlled for multiplicity. In UltIMMA-1, the proportion of patients who achieved sPGA clear or almost clear at week 52 was 86.2% for those who continued treatment with risankizumab and 54% for those who continued with ustekinumab (adjusted difference: 32.4; 95% CI, 22.0 to 42.9; *P* < 0.001). In UltIMMA-2, 83.3% who continued treatment with risankizumab and 54.5% of those who continued with ustekinumab achieved sPGA clear or almost clear at week 52 (adjusted difference: 29.1; 95% CI, 18.5 to 39.6; *P* < 0.001). The proportion of patients who achieved sPGA clear or almost clear in the group randomized to placebo in Part A and switched to risankizumab in Part B was 90.4% in UltIMMA-1 and 87.2% in UltIMMA-2. The proportion of patients who achieved sPGA clear at week 52 was a ranked secondary end point and was statistically significantly greater in patients who continued treatment with risankizumab compared with ustekinumab in UltIMMA-1 (57.6% versus 21.0%, adjusted difference: 36.5; 95% CI, 27.0 to 45.9); *P* < 0.001) and UltIMMA-2 (59.5% versus 30.3%, adjusted difference: 29.5; 95% CI, 18.9 to 40.1; *P* < 0.001). The proportion of patients who achieved sPGA clear in the group randomized to placebo in Part A and switched to risankizumab in Part B was 54.6% in UltIMMA-1 and 67.0% in UltIMMA-2; no statistical comparisons were conducted against this group. Results of sPGA outcomes at week 52 in UltIMMA-1 and UltIMMA-2 are summarized in Table 14.

In IMMhance, the key end point for Part B was the proportion of patients in the ITT_B_R population who achieved sPGA clear or almost clear at week 52. The proportion of patients who achieved sPGA clear or almost clear at week 52 in the ITT_B_R population was statistically significantly greater in patients who continued risankizumab compared with patients who switched to placebo (87.4% versus 61.3%; adjusted difference: 34.2%; 95% CI, 23.7 to 44.7; *P* < 0.001). The ranked secondary end point for Part B of IMMhance is sPGA clear or almost clear at week 104, which has not been reached, as the study is ongoing. Remaining outcomes described for sPGA in Part B of the IMMhance study were not controlled for multiplicity. The proportion of patients who achieved sPGA clear at week 52 in the ITT_B_R population was 64.9% for patients who continued on risankizumab versus 30.7% for patients switched to placebo. A total of 85% of patients switched to placebo who experienced a relapse and were re-treated with open-label risankizumab achieved sPGA clear or almost clear at week 16 of re-treatment. An sPGA of clear at

week 16 of re-treatment was achieved in 35.0% of this patient population. A summary of these results is presented in Table 25.

In IMMvent, sPGA outcomes in Part B were not included in the ranked hierarchy for the statistical analysis and were not controlled for multiplicity. In the ITT_B_RR population, 33.9% of patients re-randomized to adalimumab and 73.6% of patients re-randomized to risankizumab in Part B achieved sPGA clear or almost clear at week 44 (adjusted difference: 38.9; 95% CI, 22.0 to 55.8; $P < 0.001$; Table 15). Further, 7.1% of patients re-randomized to adalimumab and 39.6% of patients re-randomized to risankizumab in Part B achieved sPGA clear at week 52 (adjusted difference: 32.8; 95% CI, 18.8 to 46.9; $P < 0.001$). The proportion of patients achieving sPGA clear or almost clear sPGA clear was also measured at week 44 in the ITT_B_R population (79.9% and 49.3%, respectively), ITT_B_NR population (63.2% and 36.8%, respectively), and ITT_B_RZB population (77.7% and 52.2%, respectively); see Table 26 for a summary of results.

Patient-Reported Outcomes

Psoriasis Symptoms Scale

As shown in Table 13, in Part A of UltIMMA-1 and UltIMMA-2, statistically significant improvements in PSS were observed in patients treated with risankizumab over placebo at week 16. In UltIMMA-1, the proportion of risankizumab-treated patients who achieved a PSS score of 0 at week 16 was 29.3% compared with 2.0% of placebo-treated patients (adjusted difference: 27.1%, 95% CI, 21.2 to 32.9; $P < 0.001$). In UltIMMA-2, the proportion of risankizumab-treated patients who achieved a PSS score of 0 at week 16 was 31.3% compared with 0% of placebo-treated patients (adjusted difference: 31.2%, 95% CI, 25.7 to 36.69; $P < 0.001$). The proportion of patients who achieved a PSS score of 0 at week 16 in the ustekinumab group was 15.0% in UltIMMA-1 and 15.2% in UltIMMA-2; the comparison between the risankizumab and ustekinumab groups was not included in the statistical analysis hierarchy in either study.

As shown in Table 14, in Part B of UltIMMA-1, the proportion of patients who achieved a PSS score of 0 at week 52 was statistically significantly greater in the risankizumab group compared with the ustekinumab group (56.9% versus 30.0%, adjusted difference: 27.0; 95% CI, 16.7 to 37.3; $P < 0.001$); 50.5% of patients in the placebo group achieved a PSS score of 0 at week 52. In Part B of UltIMMA-2, the proportion of patients who achieved a PSS score of 0 at week 52 was also statistically significantly greater in the risankizumab group compared with the ustekinumab group (54.4 versus 30.3, adjusted difference: 24.2; 95% CI, 13.8 to 34.7; $P < 0.001$); 47.9% of patients in the placebo group achieved a PSS score of 0 at week 52. The PSS score in Part B was outside the statistical testing hierarchy for both studies and was not controlled for multiplicity; therefore, these results should be interpreted with consideration of the risk of type I error. No statistical comparisons between risankizumab and placebo were conducted for PSS at week 52.

PSS was not measured in Part A or Part B of either the IMMhance or IMMvent study.

Table 13: Key Efficacy Outcomes at Week 16 (Intention-to-Treat Population)

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
	PBO (N = 102)	UST (N = 100)	RZB (N = 304)	PBO (N = 98)	UST (N = 99)	RZB (N = 294)	PBO (N = 100)	RZB (N = 407)	ADA (N = 304)	RZB (N = 301)
Proportion of Patients Achieving a DLQI Score of 0 or 1 at Week 16 (NRI)										
n (%)	8 (7.8)	43 (43.0)	200 (65.8)	4 (4.1)	46 (46.5)	196 (66.7)	3 (3.0)	266 (65.4)	148 (48.7)	198 (65.8)
Adjusted difference vs. RZB (95% CI)	57.9 (50.4 to 65.3)	23.0 (11.9 to 34.0)	–	62.2 (55.5 to 68.9)	20.2 (9.1 to 31.4)	–	62.1 (56.4 to 67.9)	–	17.1 (9.3 to 24.8)	–
P value	< 0.001	< 0.001	–	< 0.001	< 0.001	–	< 0.001	–	< 0.001	–
DLQI Change From Baseline to Week 16 (LOCF)										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	288	285
Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13.1	14.2
Week 16, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.4	1.8
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	−9.7 (0.29)	−11.5 (0.30)
Treatment difference, LS mean (SE) vs. RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	−2.5 to −1.1	–
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	< 0.001	–
Proportion of Patients Achieving PASI 90 at Week 16 (NRI)										
n (%)	5 (4.9)	42 (42.0)	229 (75.3)	2 (2.0)	47 (47.5)	220 (74.8)	2 (2.0)	298 (73.2)	144 (47.4)	218 (72.4)
Adjusted difference vs. RZB (95% CI)	70.3 (64.0 to 76.7)	33.5 (22.7 to 44.3)	–	72.5 (66.8 to 78.2)	27.6 (16.7 to 38.5)	–	[redacted]	[redacted]	24.9 (17.5 to 32.4)	–
P value	< 0.001	< 0.001	–	< 0.001	< 0.001	–	< 0.001	–	< 0.001	–
Proportion of Patients Achieving PASI 100 at Week 16 (NRI)										
n (%)	0	12 (12.0)	109 (35.9)	2 (2.0)	24 (24.2)	149 (50.7)	1 (1.0)	192 (47.2)	70 (23.0)	120 (39.9)
Adjusted difference vs. RZB (95% CI)	35.5 (30.0 to 41.0)	23.8 (15.5 to 32.1)	–	48.2 (41.9 to 54.6)	27.0 (17.0 to 37.0)	–	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.001	< 0.001	–	< 0.001	< 0.001	–	< 0.001	–	< 0.001	–

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
	PBO (N = 102)	UST (N = 100)	RZB (N = 304)	PBO (N = 98)	UST (N = 99)	RZB (N = 294)	PBO (N = 100)	RZB (N = 407)	ADA (N = 304)	RZB (N = 301)
Proportion of Patients Achieving an sPGA Score of 0 or 1 (Clear or Almost Clear) at Week 16 (NRI)										
n (%)	8 (7.8)	63 (63.0)	267 (87.8)	5 (5.1)	61 (61.6)	246 (83.7)	7 (7.0)	340 (83.5)	183 (60.2)	252 (83.7)
Adjusted difference vs. RZB (95% CI)	79.9 (73.5 to 86.3)	25.1 (15.2 to 35.0)	–	78.5 (72.4 to 84.5)	22.3 (12.0 to 32.5)	–	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.001	< 0.001	–	< 0.001	< 0.001	–	< 0.001	–	< 0.001	–
Proportion of Patients Achieving an sPGA Score of 0 (Clear) at Week 16 (NRI)										
n (%)	2 (2.0)	14 (14.0)	112 (36.8)	3 (3.1)	25 (25.3)	150 (51.0)	1 (1.0)	189 (46.4)	[redacted]	[redacted]
Adjusted difference vs. RZB (95% CI)	34.7 (28.6 to 40.8)	22.9 (14.3 to 31.6)	–	47.5 (40.9 to 54.2)	26.3 (16.1 to 36.4)	–	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.001	< 0.001	–	< 0.001	< 0.001	–	< 0.001	—	[redacted]	[redacted]
Proportion of Patients Achieving a PSS Score of 0 at Week 16 (NRI)										
n (%)	2 (2.0)	15 (15.0)	89 (29.3)	0	15 (15.2)	92 (31.3)	NR	NR	NR	NR
Adjusted difference vs. RZB (95% CI)	27.1 (21.2 to 32.9)	14.3 (5.8 to 22.8)	–	31.2 (25.7 to 36.6)	16.1 (7.5 to 24.8)	–				
P value	< 0.001	< 0.001	–	< 0.001	< 0.001	–				

ADA = adalimumab; CI = confidence interval; DLQI = Dermatology Life Quality Index; ITT = intention-to-treat; LOCF = last observation carried forward; NR = not reported; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; PSS = Psoriasis Symptoms Scale; RZB = risankizumab; SE = standard error; sPGA = static Physician Global Assessment; UST = ustekinumab; vs. = versus.

Note: For Part A, CI and *P* values are computed for comparison between RZB versus UST, and RZB versus PBO. Across the strata, 95% CI for adjusted difference was calculated according to the Cochran–Mantel–Haenszel test adjusted for the comparison of two treatment groups. If there was a stratum containing zero count, 0.1 was added to each cell. Within each stratum, the 95% CI for difference was calculated based on normal approximation to the binomial distribution. Across the strata; *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata. If there was a stratum containing zero count, 0.1 was added to each cell.

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Table 14: Key Efficacy Outcomes at Week 52 — UltIMMA-1 and UltIMMA-2 (Intention-to-Treat Population)

	UltIMMA-1			UltIMMA-2		
	PBO/RZB (N = 97)	UST/UST (N = 100)	RZB/RZB (N = 304)	PBO/RZB (N = 94)	UST/UST (N = 99)	RZB/RZB (N = 294)
Proportion of Patients Achieving a DLQI Score of 0 or 1 at Week 52 (NRI)						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference vs. RZB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI Change From Baseline to Week 52 (LOCF)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference, LS mean (SE) vs. RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of Patients Achieving PASI 90 at Week 52 (NRI)						
n (%)	76 (78.4)	44 (44.0)	249 (81.9)	80 (85.1)	50 (50.5)	237 (80.6)
Adjusted difference vs. RZB (95% CI)	–	38.3 (27.9 to 48.6)	–	–	30.2 (19.6 to 40.9)	–
P value	–	< 0.001	–	–	< 0.001	–
Proportion of Patients Achieving PASI 100 at Week 52 (NRI)						
n (%)	53 (54.6)	21 (21.0)	171 (56.3)	63 (67.0)	30 (30.3)	175 (59.5)
Adjusted difference vs. RZB (95% CI)	–	35.1 (25.7 to 44.6)	–	–	29.5 (18.9 to 40.1)	–
P value	–	< 0.001	–	–	< 0.001	–
Proportion of Patients Achieving an sPGA Score of 0 or 1 (Clear or Almost Clear) at Week 52 (NRI)						
n (%)	88 (90.7)	54 (54.0)	262 (86.2)	82 (87.2)	54 (54.5)	245 (83.3)
Adjusted difference vs. RZB (95% CI)	–	32.4 (22.0 to 42.9)	–	–	29.1 (18.5 to 39.6)	–
P value	–	< 0.001	–	–	< 0.001	–
Proportion of Patients Achieving an sPGA Score of 0 (Clear) at Week 52 (NRI)						
n (%)	53 (54.6)	21 (21.0)	175 (57.6)	63 (67.0)	30 (30.3)	175 (59.5)
Adjusted difference vs. RZB (95% CI)	–	36.5 (27.0 to 45.9)	–	–	29.5 (18.9 to 40.1)	–
P value	–	< 0.001	–	–	0.001	–
Proportion of Patients Achieving a PSS Score of 0 at Week 52 (NRI)						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference vs. RZB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	UltIMMA-1			UltIMMA-2		
	PBO/RZB (N = 97)	UST/UST (N = 100)	RZB/RZB (N = 304)	PBO/RZB (N = 94)	UST/UST (N = 99)	RZB/RZB (N = 294)
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DLQI = Dermatology Life Quality Index; ITT = intention-to-treat; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; PSS = Psoriasis Symptoms Scale; RZB = risankizumab; SE = standard error; sPGA = static Physician Global Assessment; UST = ustekinumab; vs. = versus.

Note: Across the strata, 95% CI for adjusted difference was calculated according to the Cochran–Mantel–Haenszel test adjusted for the comparison of two treatment groups. If there was a stratum containing zero count, 0.1 was added to each cell. Within each stratum, the 95% CI for difference was calculated based on normal approximation to the binomial distribution. Across the strata; *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata.

Source: UltIMMA-1[20] and UltIMMA-2[21] Clinical Study Reports.

Table 15: Key Efficacy Outcomes at WEEK 44 — IMMvent (ITT_B_RR Population)

	IMMvent	
	ADA/ADA (N = 56)	ADA/RZB (N = 53)
Proportion of Patients Achieving a DLQI Score of 0 or 1 at Week 44 (NRI)		
n (%)	[redacted]	[redacted]
Adjusted difference (95% CI)	[redacted]	
P value	[redacted]	
DLQI Change From Baseline to Week 44 (LOCF)		
N	[redacted]	[redacted]
Baseline, mean	[redacted]	[redacted]
Week 44, mean	[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]
Treatment difference, LS mean (SE) vs. RZB	[redacted]	
95% CI	[redacted]	
P value	[redacted]	
Proportion of Patients Achieving PASI 90 at Week 44 (NRI)		
n (%)	12 (21.4)	35 (66.0)
Adjusted difference (95% CI)	45.0 ([redacted])	
P value	< 0.001	
Proportion of Patients Achieving PASI 100 at Week 44 (NRI)		
n (%)	4 (7.1)	21 (39.6)
Adjusted difference (95% CI)	32.8 ([redacted])	
P value	< 0.001	
Proportion of Patients Achieving an sPGA Score of 0 or 1 (Clear or Almost Clear) at Week 44 (NRI)		
n (%)	19 (33.9)	39 (73.6)
Adjusted difference (95% CI)	38.9 (22.0 to 55.8)	
P value	< 0.001	
Proportion of Patients Achieving an sPGA Score of 0 (Clear) at Week 44 (NRI)		
n (%)	4 (7.1)	21 (39.6)

	IMMvent	
	ADA/ADA (N = 56)	ADA/RZB (N = 53)
Adjusted difference (95% CI)	32.8 ([redacted])	
P value	< 0.001	

ADA = adalimumab; CI = confidence interval; DLQI = Dermatology Life Quality Index; ITT_B_RR = intention-to-treat population in Part B who were re-randomized; LS = least squares; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; RZB = risankizumab; SE = standard error; sPGA = static Physician Global Assessment.

Note: The ITT_B_RR population includes all patients who were randomized to adalimumab at baseline in Part A and re-randomized at week 16.

Across the strata, 95% CI for adjusted difference was calculated according to the Cochran–Mantel–Haenszel test for the comparison of two treatment groups. If there is a stratum containing zero count, 0.1 will be added to each cell. Across the strata; *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata.
Source: IMMvent Clinical Study Report.[23]

Harms

Only those harms identified in the CDR review protocol (Table 3) are reported subsequently. Harms are presented separately for each study using the safety analysis set defined for each study population. See Table 16 through Table 19 for detailed harms data.

Adverse Events

In UltIMMA-1 during Part A, AEs occurred in a similar proportion of patients across treatment groups with 51%, 50%, and 49.7% of patients reporting AEs in the placebo, ustekinumab, and risankizumab groups, respectively. In Part B, the proportion of patients with AEs was slightly lower in patients who continued treatment with risankizumab (61.3%) than in those who continued treatment with ustekinumab (66.7%) and those who switched from placebo to risankizumab at week 16 (67.0%). The proportion of patients with AEs who received continuous treatment with risankizumab or ustekinumab from week 0 to 52 was 72.7% in the risankizumab group and 77% in the ustekinumab group. A summary of AEs reported by at least 3% of patients is provided in Table 16. The most frequently reported AEs across all parts of the study were upper respiratory tract infection ([redacted]) and viral respiratory tract infection ([redacted]), which were more common in the ustekinumab group than in the risankizumab group, respectively. In general, the AE profile was similar between the risankizumab and ustekinumab groups.

In UltIMMA-2 during Part A, the proportion of patients with AEs in the risankizumab group (45.6%) was slightly lower than in the ustekinumab group (53.5%) and similar to placebo (45.9%). In Part B, the proportion of patients with AEs was lower in patients who continued treatment with risankizumab (55.7%) than in those who continued treatment with ustekinumab (74.5%) and those who switched from placebo to risankizumab at week 16 (64.9%). The proportion of AEs in patients who received continuous treatment with risankizumab or ustekinumab from week 0 to 52 was 67.3% in the risankizumab group and 80.8% in the ustekinumab group. A summary of AEs reported by at least 3% of patients is provided in Table 17. Similar to UltIMMA-1, the most frequently reported AEs across all parts of the UltIMMA-2 were upper respiratory tract infection ([redacted]) and viral respiratory tract infection ([redacted]), which were more common in the ustekinumab group than in the risankizumab group, respectively. [redacted]) were more common in the ustekinumab group than in the risankizumab group. Arthralgia was reported by a [redacted] group.

A summary of AEs reported by at least 3% of patients in the IMMhance study is provided in Table 18. AEs occurred in a similar proportion of patients in the risankizumab (45.5%) and placebo (48.0%) groups from week 0 to 16. A similar proportion of patients experienced AEs during Part B in the Safety_B_R population (patients randomized to risankizumab in Part A and re-randomized to continue risankizumab [70.3%] or switched to placebo [64.4%] at week 28). The most frequently reported AEs during the study were [redacted], which occurred in a similar proportion of patients in both treatment groups; [redacted] was also commonly reported during Part B.

A summary of AEs reported by at least 3% of patients in the IMMvent study is provided in Table 19. In Part A, AEs occurred in a similar proportion of patients in the risankizumab (55.8%) and adalimumab (56.9%) groups. The most frequently reported AEs were [redacted] and [redacted] which were more common in the risankizumab group than in the adalimumab group, respectively. Headache occurred in a [redacted] group. In part B in the Safety B_RR population, AEs were reported in a higher proportion of patients re-randomized to risankizumab (75.5%) than in patients re-randomized to adalimumab (66.1%). [redacted] were the most commonly reported AEs reported for the risankizumab and adalimumab groups, respectively.

Serious Adverse Events

SAEs occurred infrequently regardless of the treatment period and treatment group in all four included trials. No SAE was observed in more than two patients in any study.

In Part A of UltIMMA-1, the proportion of patients with SAEs was higher in the ustekinumab group (8.0%) than in the risankizumab (2.3%) or placebo (2.9%) groups (Table 16). The proportion of patients with SAEs in Part B was similar in patients who continued treatment with risankizumab (5.4%), those who continued treatment with ustekinumab (4.0%), and those who were switched from placebo to risankizumab at week 16 (4.0%). The proportion of patients who experienced an SAE was slightly lower in patients who received continuous treatment with risankizumab (7.6%) compared with those who received ustekinumab (11.0%) from week 0 to 52.

In UltIMMA-2, the proportion of patients who experienced an SAE was generally similar throughout the study. In Part A, SAEs were experienced by 2.0% of patients in the risankizumab group, 3.0% in the ustekinumab group, and 1.0% in the placebo group (Table 17). In Part B, the proportion of patients with SAEs was 4.5% in patients who continued treatment with risankizumab, 4.3% in those who continued treatment with ustekinumab, and 3.2% in those who switched from placebo to risankizumab at week 16. The proportion of patients who experienced an SAE was similar in patients who received continuous treatment with risankizumab (6.5%) to those who received ustekinumab (7.1%) from week 0 to 52.

In IMMhance, during Part A, a lower proportion of patients experienced an SAE in the risankizumab group (2.0%) compared with the placebo group (8%). No SAE was reported by more than one patient in either treatment group. In Part B, the proportion of patients with SAEs was similar in the Safety_B_R population (6.3% in patients who continued treatment

with risankizumab and 6.2% in patients switched from risankizumab to placebo). In general, treatment with risankizumab did not appear to result in any clinically meaning safety signals compared with placebo.

In IMMvent, the proportion of patients who experienced SAEs was similar between the risankizumab (3.3%) and adalimumab (3.0%) groups. In Part B in the Safety_B_RR population, SAEs were reported in a higher proportion of patients re-randomized to risankizumab (5.7%) compared with those re-randomized to adalimumab (3.6%). No SAE was reported by more than one patient in either treatment group (with the exception of a suicide attempt, which was reported for one patient in each treatment group).

Withdrawals Due to Adverse Events

Details of withdrawals due to adverse events were not provided for any of the trials included in this review.

In UltIMMA-1, the rate of study withdrawal due to AEs was low: 2.0%, 0%, and 0.3% in the placebo, ustekinumab, and risankizumab groups, respectively, during Part A, and 0%, 2.0%, and 0.3% in the patients who were switched from placebo to risankizumab, continued ustekinumab, and continued risankizumab, respectively, during Part B (Table 16).

In UltIMMA-2, 1.0% of patients in the placebo group withdrew due to AEs during Part A; no patients in the ustekinumab or risankizumab groups withdrew during this time. During Part B, 1.1%, 1.0%, and 0.3% of patients who were switched from placebo to risankizumab, continued ustekinumab, and continued risankizumab, respectively, withdrew from the study due to AEs during Part B (Table 17).

In IMMhance, 1.0% of patients in the placebo group and 0.2% of patients in the risankizumab group withdrew from the study due to AEs during the double-blind treatment period in Part A. In Part B in the Safety_B_R population, 1.8% of patients who continued risankizumab and 0.9% of patients switched to placebo withdrew due to AEs (Table 18).

In IMMvent the proportion of withdrawals due to AEs was low and consistent across both parts of the study and across safety sets. A higher proportion of patients in the adalimumab group withdrew from the study due to AEs in Part A than the risankizumab group (2.3% versus 1.0%, respectively). In patients who were considered inadequate responders to adalimumab and who were re-randomized in Part B, 3.6% of the patients who were re-randomized to continue on adalimumab withdrew due to AEs, while no patients re-randomized to risankizumab withdrew (Table 19).

Mortality

No deaths occurred during UltIMMA-1.

In UltIMMA-2, two (0.7%) deaths occurred during the study; both patients had been treated with risankizumab. One death was due to sudden cardiac death and cause of death was undetermined in the other patient.

In IMMhance, no patients died during the double-blind period of Part A. [redacted].

There was a total of three deaths during the IMMvent study, all of which occurred during Part A. One death occurred in the risankizumab group and was due to acute myocardial infarction. Two deaths occurred in the adalimumab group: one death was due to gallbladder cancer and the other from abdominal abscess and sepsis.

Notable Harms

Notable harms identified in the CDR review protocol included infections, injection-site reactions, hypersensitivity events, immunogenicity, inflammatory bowel disease, major cardiovascular events (MACE), and psychiatric symptoms and are summarized in Table 16, Table 17, Table 18, and Table 19 for UltIMMA-1, UltIMMA-2, IMMhance, and IMMvent, respectively.

In general, the rate of infections was low in each of the trials. The frequency of serious infection varied across trials and between treatment groups, but fungal infections were more common in patients treated with risankizumab. None of the fungal infections were considered to be SAEs. Throughout UltIMMA-1, the proportion of patients experiencing serious infections was slightly higher in the ustekinumab (3.0%) than in the risankizumab (1.0%) group, and a higher proportion of patients reported fungal infections in the risankizumab (4.6%) group than in the ustekinumab (1.0%) group. Throughout UltIMMA-2, the proportion of patients experiencing serious infections was similar in the risankizumab (1.7%) and ustekinumab (1.0%) groups and a higher proportion of patients reported fungal infections in the risankizumab (3.4%) group than in the ustekinumab (1.0%) group. In IMMhance, the proportion of patients who experienced infections was similar between the risankizumab and placebo groups during the double-blind treatment period in Part A. [redacted]. The proportion of patients who experienced infections was similar between the risankizumab and placebo groups during Part A of the IMMvent study, and the incidence of [redacted]. In Part B in the Safety_B_RR population, a higher proportion of patients re-randomized to risankizumab experienced serious infections (3.8%) than patients re-randomized to adalimumab (no patients).

The proportion of patients experiencing injection-site reactions was [redacted].

[redacted]

[redacted].

Incidence of inflammatory bowel disease was not reported in any of the studies.

In general, the frequency of MACE was low in each of the trials included in this review. No MACE were reported during UltIMMA-1. In UltIMMA-2, two patients experienced MACE during Part B (including one death and one myocardial infarction), both of which were in the risankizumab group. In IMMhance, a total of two patients experienced MACE: in Part A, one patient in the placebo group had a stroke, [redacted]. A total of two patients experienced MACE during IMMvent; both were adjudicated as myocardial infarction. One occurred during Part A in a patient in the risankizumab group, and the other event occurred in one patient identified as a nonresponder to adalimumab during Part A who switched to treatment with risankizumab (Safety_B_NR population), which resulted in death.

No clear pattern of psychiatric symptoms emerged with risankizumab during UltIMMA-1, UltIMMA-2, IMMhance, or IMMvent. [redacted].

Immunogenicity

In UltIMMA-1 and UltIMMA-2, the incidence of anti-drug antibodies and neutralizing antibodies (NAb) was [redacted] at week 16 and 52.

As shown in Table 20, in IMMhance, the incidence of treatment-emergent anti-drug antibodies and NAb was [redacted].

In IMMvent, the incidence of treatment-emergent anti-drug antibodies and NAb was [redacted].

Table 16: Harms: UltIMMA-1

	Part A (Week 0 to 16)			Part B (Week 16 to 52)			Parts A and B (Week 0 to 52)		All RZB (N = 401)
	PBO (N = 102)	UST (N = 100)	RZB (N = 304)	PBO/RZB (N = 97)	UST/UST (N = 99)	RZB/RZB (N = 297)	UST/ UST (N = 100)	RZB/RZB (N = 304)	
Patients with > 0 AEs, N (%)	52 (51.0)	50 (50.0)	151 (49.7)	65 (67.0)	66 (66.7)	182 (61.3)	77 (77.0)	221 (72.7)	286 (71.3)
Most Common AEs[a]									
Diarrhea							[redacted]	[redacted]	
Gastroesophageal reflux disease				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
Injection-site reaction	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	
Bronchitis				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Folliculitis							[redacted]	[redacted]	
Gastroenteritis				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Influenza							[redacted]	[redacted]	
Nasopharyngitis				[redacted]	[redacted]	[redacted]			
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase in blood creatinine phosphokinase							[redacted]	[redacted]	
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthritis							[redacted]	[redacted]	
Back pain							[redacted]	[redacted]	
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	
Psoriasis	[redacted]	[redacted]	[redacted]						

	Part A (Week 0 to 16)			Part B (Week 16 to 52)			Parts A and B (Week 0 to 52)		All RZB (N = 401)
	PBO (N = 102)	UST (N = 100)	RZB (N = 304)	PBO/RZB (N = 97)	UST/UST (N = 99)	RZB/RZB (N = 297)	UST/ UST (N = 100)	RZB/RZB (N = 304)	
Hypertension				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Insomnia				[redacted]	[redacted]	[redacted]			
Patients with > 0 SAEs, N (%)	3 (2.9)	8 (8.0)	7 (2.3)	3 (3.1)	4 (4.0)	16 (5.4)	11 (11.0)	23 (7.6)	26 (6.5)
Withdrawals due to AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, N (%)	0	0	0	0	0	0	0	0	0
Notable Harms, N (%)									
Infections									
Serious infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fungal infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Inflammatory bowel disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major cardiovascular events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric symptoms									
Acute psychosis				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bipolar disorder				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed mood	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Part A (Week 0 to 16)			Part B (Week 16 to 52)			Parts A and B (Week 0 to 52)		All RZB (N = 401)
	PBO (N = 102)	UST (N = 100)	RZB (N = 304)	PBO/RZB (N = 97)	UST/UST (N = 99)	RZB/RZB (N = 297)	UST/ UST (N = 100)	RZB/RZB (N = 304)	
Panic attack				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Schizoaffective disorder				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Suicidal ideation	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	
Stress				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; PBO = placebo; RZB = risankizumab; SAE = serious adverse event; UST = ustekinumab.

Note: The All Risankizumab group included patients who received at least one dose of risankizumab during the study.

[a] Frequency > 3%.

Source: UltIMMA-1 Clinical Study Report.[20]

Table 17: Harms: UltIMMA-2

	Part A (Week 0 to 16)			Part B (Week 16 to 52)			Parts A and B (Week 0 to 52)		All RZB (N = 388)
	PBO (N = 98)	UST (N = 99)	RZB (N = 294)	PBO/RZB (N = 94)	UST/UST (N = 94)	RZB/RZB (N = 291)	UST/UST (N = 99)	RZB/RZB (N = 294)	
Patients with > 0 AEs, N (%)	45 (45.9)	53 (53.5)	134 (45.6)	61 (64.9)	70 (74.5)	162 (55.7)	80 (80.8)	198 (67.3)	259 (66.8)
Most Common AEs[a]									
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Vomiting							[redacted]	[redacted]	
Bronchitis							[redacted]	[redacted]	
Folliculitis				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Furuncle							[redacted]	[redacted]	
Influenza				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Oral herpes							[redacted]	[redacted]	
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Part A (Week 0 to 16)			Part B (Week 16 to 52)			Parts A and B (Week 0 to 52)		All RZB (N = 388)
	PBO (N = 98)	UST (N = 99)	RZB (N = 294)	PBO/RZB (N = 94)	UST/UST (N = 94)	RZB/RZB (N = 291)	UST/UST (N = 99)	RZB/RZB (N = 294)	
Urinary tract infection	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ligament sprain							[redacted]	[redacted]	
Limb injury							[redacted]	[redacted]	
Increased blood creatinine phosphokinase				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Arthralgia	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
Arthritis									
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Myalgia							[redacted]	[redacted]	
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinus congestion				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Erythema							[redacted]	[redacted]	
Pruritus	[redacted]	[redacted]	[redacted]						
Psoriasis	[redacted]	[redacted]	[redacted]						
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 SAEs, N (%)	1 (1.0)	3 (3.0)	6 (2.0)	3 (3.2)	4 (4.3)	13 (4.5)	7 (7.1)	19 (6.5)	22 (5.7)
Withdrawals due to AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Deaths, N (%)	0	0	1 (0.3)	0	0	1 (0.3)	0	2 (0.7)	2 (0.5)
Notable Harms, N (%)									
Infections									
Serious infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Part A (Week 0 to 16)			Part B (Week 16 to 52)			Parts A and B (Week 0 to 52)		All RZB (N = 388)
	PBO (N = 98)	UST (N = 99)	RZB (N = 294)	PBO/RZB (N = 94)	UST/UST (N = 94)	RZB/RZB (N = 291)	UST/UST (N = 99)	RZB/RZB (N = 294)	
Tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fungal infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inflammatory bowel disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major cardiovascular events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric Symptoms									
Adjustment disorder with depressed mood	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	
Affective disorder				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sleep disorder	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
Stress	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; PBO = placebo; RZB = risankizumab; SAE = serious adverse event; UST = ustekinumab.

[a] Frequency > 3%.

Note: The All Risankizumab group included patients who received at least one dose of risankizumab during the study.

Source: UltIMMA-2 Clinical Study Report.[21]

Table 18: Harms: IMMhance

	Part A1 (Week 0 to 16)		Part B (Week 28 to 52)				
	PBO (N = 100)	RZB (N = 407)	Safety_B_R		Safety_B_NR RZB/RZB/RZB (N = 63)	Safety_B_PBO_RT RZB/RZB/PBO/RZB (N = 40)	All RZB (N = 500)
			RZB/RZB/ PBO (N = 225)	RZB/RZB/RZB (N = 111)			
Patients with > 0 AEs, N (%)	48 (48.0)	185 (45.5)	145 (64.4)	78 (70.3)	48 (76.2)	15 (37.5)	387 (77.4)
Most Common AEs[a]							
Diarrhea							[redacted]
Gastroesophageal reflux disease					[redacted]		
Influenza			[redacted]	[redacted]	[redacted]		[redacted]
Nasopharyngitis							
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Urinary tract infection					[redacted]		[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Contusion					[redacted]		
Muscle strain					[redacted]		
Gamma-glutamyltransferase increased					[redacted]		
Diabetes mellitus					[redacted]		
Hypercholesterolemia					[redacted]		
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Arthritis							
Back pain			[redacted]	[redacted]	[redacted]		[redacted]
Muscle spasms					[redacted]		
Pain in extremity					[redacted]		
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Anxiety					[redacted]		

	Part A1 (Week 0 to 16)		Part B (Week 28 to 52)				
	PBO (N = 100)	RZB (N = 407)	Safety_B_R		Safety_B_NR RZB/RZB/RZB (N = 63)	Safety_B_PBO_RT RZB/RZB/PBO/RZB (N = 40)	All RZB (N = 500)
			RZB/RZB/ PBO (N = 225)	RZB/RZB/RZB (N = 111)			
Cough			[redacted]	[redacted]			
Dermatitis contact						[redacted]	
Dermal cyst					[redacted]		
Pruritus			[redacted]	[redacted]	[redacted]		
Psoriasis	[redacted]	[redacted]					
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
Patients with > 0 SAEs, N (%)	8 (8.0)	8 (2.0)	14 (6.2)	7 (6.3)	5 (7.9)	0	35 (7.0)
Withdrawals due to AEs, N (%)	1 (1.0)	1 (0.2)	2 (0.9)	2 (1.8)	1 (1.6)	Not reported	Not reported
Deaths, N (%)	0	0	0	1 (0.9)	0	0	2 (0.4)
Notable Harms, N (%)							
Infections							
Serious infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fungal infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inflammatory bowel disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major cardiovascular events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric Symptoms							
Agitation	[redacted]	[redacted]				[redacted]	[redacted]
Alcoholism	[redacted]	[redacted]					
Agitation							[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

	Part A1 (Week 0 to 16)		Part B (Week 28 to 52)				
	PBO (N = 100)	RZB (N = 407)	Safety_B_R RZB/RZB/ PBO (N = 225)	Safety_B_R RZB/RZB/RZB (N = 111)	Safety_B_NR RZB/RZB/RZB (N = 63)	Safety_B_PBO_RT RZB/RZB/PBO/RZB (N = 40)	All RZB (N = 500)
Delirium tremens					[redacted]		[redacted]
Depressed mood	[redacted]	[redacted]					[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Emotional distress							[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]			
Self-injurious ideation	[redacted]	[redacted]					[redacted]
Suicidal ideation	[redacted]	[redacted]	[redacted]	[redacted]			
Stress							[redacted]

AE = adverse event; PBO = placebo; RZB = risankizumab; SAE = serious adverse event.

Note: The Safety_B_R population included patients who were considered responders and re-randomized.
The Safety_B_NR population included patients who were randomized to risankizumab at baseline, were considered nonresponders, and received risankizumab during Part B.
The Safety_B_PBO_RT population included patients re-randomized to placebo during Part B and re-treated with risankizumab after relapse.
The All_RZB population included patients who received at least one dose of risankizumab during the study.

[a] Frequency > 3%.

Source: IMMhance Clinical Study Report.[22]

Table 19: Harms: IMMvent

	Part A (Week 0 to 16)		Part B					
	ADA (N = 304)	RZB (N = 301)	(Safety _B_RR) ADA/ADA (N = 56)	(Safety _B_RR) ADA/RZB (N = 53)	Safety_B_R ADA/ADA (N = 144)	Safety_B_NR ADA/RZB (N = 38)	Safety_B_RZB RZB/RZB (N = 294)	All RZB (N = 392)
Patients with > 0 AEs, N (%)	173 (56.9)	168 (55.8)	37 (66.1)	40 (75.5)	98 (68.1)	23 (60.5)	188 (63.9)	293 (74.7)
Most Common AEs[a]								
Vertigo			[redacted]	[redacted]				
Diarrhea			[redacted]	[redacted]				
Food poisoning			[redacted]	[redacted]				

	Part A (Week 0 to 16)		Part B					
	ADA (N = 304)	RZB (N = 301)	(Safety _B_RR) ADA/ADA (N = 56)	(Safety _B_RR) ADA/RZB (N = 53)	Safety_B_R ADA/ADA (N = 144)	Safety_B_NR ADA/RZB (N = 38)	Safety_B_RZB RZB/RZB (N = 294)	All RZB (N = 392)
Hematochezia			[redacted]	[redacted]				
Fatigue	[redacted]	[redacted]						[redacted]
Bronchitis			[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Folliculitis			[redacted]	[redacted]				
Periodontitis			[redacted]	[redacted]				
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection			[redacted]	[redacted]				[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased			[redacted]	[redacted]	[redacted]			
Aspartate aminotransferase increased			[redacted]	[redacted]				
Hypertriglyceridemia			[redacted]	[redacted]				
Seborrheic keratosis						[redacted]		
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]
Intervertebral disc protrusion			[redacted]	[redacted]				
Myalgia			[redacted]	[redacted]				
Psoriatic arthropathy			[redacted]	[redacted]				
Dizziness			[redacted]	[redacted]				
Headache	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]
Anxiety			[redacted]	[redacted]				
Cough			[redacted]	[redacted]				[redacted]
Oropharyngeal pain			[redacted]	[redacted]		[redacted]		
Intertrigo			[redacted]	[redacted]				
Pruritus	[redacted]	[redacted]						[redacted]
Hypertension					[redacted]	[redacted]	[redacted]	[redacted]

	Part A (Week 0 to 16)		Part B					
	ADA (N = 304)	RZB (N = 301)	(Safety _B_RR) ADA/ADA (N = 56)	(Safety _B_RR) ADA/RZB (N = 53)	Safety_B_R ADA/ADA (N = 144)	Safety_B_NR ADA/RZB (N = 38)	Safety_B_RZB RZB/RZB (N = 294)	All RZB (N = 392)
Patients with > 0 SAEs, N (%)	9 (3.0)	10 (3.3)	2 (3.6)	3 (5.7)	5 (3.5)	4 (10.5)	12 (4.1)	27 (6.9)
Withdrawals due to AEs, N (%)	7 (2.3)	3 (1.0)	2 (3.6)	0	1 (0.7)	1 (2.6)	7 (2.4)	Not reported
Deaths, N (%)	2 (0.7)	1 (0.3)	0	0	0	0	0	1 (0.3)
Notable Harms, N (%)								
Infections								
Serious infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fungal infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inflammatory bowel disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major cardiovascular events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric Symptoms								
Affect lability					[redacted]			
Agitation								
Alcoholism					[redacted]			
Alcohol withdrawal syndrome						[redacted]		[redacted]
Anxiety			[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Depressed mood					[redacted]	[redacted]		[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Insomnia	[redacted]	[redacted]			[redacted]		[redacted]	[redacted]
Libido decreased							[redacted]	[redacted]
Panic attack			[redacted]	[redacted]				[redacted]

	Part A (Week 0 to 16)		Part B					
	ADA (N = 304)	RZB (N = 301)	(Safety _B_RR) ADA/ADA (N = 56)	(Safety _B_RR) ADA/RZB (N = 53)	Safety_B_R ADA/ADA (N = 144)	Safety_B_NR ADA/RZB (N = 38)	Safety_B_RZB RZB/RZB (N = 294)	All RZB (N = 392)
Sleep disorder							[redacted]	[redacted]
Suicide attempt	[redacted]	[redacted]						[redacted]

ADA = adalimumab; AE = adverse event; RZB = risankizumab; SAE = serious adverse event.

Note:
The Safety_B_RR population included patients initially randomized to adalimumab in Part A and re-randomized to either adalimumab or risankizumab in Part B.
The Safety_B_R population included patients initially randomized to adalimumab in Part A and were considered responders and continued with adalimumab in Part B.
The Safety_B_NR population included patients initially randomized to adalimumab in Part A who were considered nonresponders and received risankizumab in Part B. The Safety_B_RZB included patients who continuously received risankizumab during Part A and B.
The ALL_RZB population included patients who received at least one dose of risankizumab during the study.

[a] Frequency > 3%.

Source: IMMvent Clinical Study Report.[23]

Table 20: Summary of Immunogenicity to Risankizumab

	UltIMMA-1				UltIMMA-2				IMMhance			IMMvent			
	PBO[a]	UST	RZB	RZB Total	PBO[a]	UST	RZB	RZB Total	PBO[a]	RZB	PBO Withdrawal [b]	ADA	RZB	ADA to RZB	RZB Total
Week 0 to 16															
Evaluable patients, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-drug antibody incidence (treatment-emergent); N (%)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
NAb incidence (treatment-emergent); N (%)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Week 0 to 44															
Evaluable patients, N												[redacted]	[redacted]	[redacted]	[redacted]
Anti-drug antibody incidence (treatment-emergent); N (%)												[redacted]	[redacted]	[redacted]	[redacted]
NAb incidence (treatment-emergent); N (%)												[redacted]	[redacted]	[redacted]	[redacted]
Week 0 to 52															
Evaluable patients, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	
Anti-drug antibody incidence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				

	UltIMMA-1				UltIMMA-2				IMMhance			IMMvent			
	PBO[a]	UST	RZB	RZB Total	PBO[a]	UST	RZB	RZB Total	PBO[a]	RZB	PBO Withdrawal [b]	ADA	RZB	ADA to RZB	RZB Total
(treatment-emergent); N (%)															
NAb incidence (treatment-emergent); N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
Week 0 to 104[c]															
Evaluable patients, N									[redacted]	[redacted]	[redacted]			[redacted]	
Anti-drug antibody incidence (treatment-emergent); N (%)									[redacted]	[redacted]	[redacted]				
NAb incidence (treatment-emergent); N (%)									[redacted]	[redacted]	[redacted]				

ADA = adalimumab; N = number of patients in group; NAb = neutralizing antibody; PBO = placebo; RZB = risankizumab; SC = subcutaneous; UST = ustekinumab.

Note: The anti-drug antibody–evaluable patients were those with at least one reportable immunogenicity assessment for at least one sampling time during the study post-baseline. The incidence of a (treatment-emergent) anti-drug antibody produced for risankizumab was defined when: The patient was either negative for the anti-drug antibody or missing a baseline assessment (prior to the first risankizumab dose) and then tested positive for the anti-drug antibody at one or more time points post-baseline; **or** the patient tested positive for the anti-drug antibody at baseline and showed a four-fold or greater increase in titer values relative to baseline, or the titer value was 2 or greater in at least one post-dose sample and the baseline titer value was less than 1. (In this case, a four-fold increment over the midpoint of 0.5 was used.)

The NAb were summarized among all patients with the (treatment-emergent) anti-drug antibody; the NAb was assessed only when the anti-drug antibody assessment was positive. NAb positive: At least one positive NAb assessment at any visit.

[a] Patients randomized to placebo at baseline and switched to risankizumab at week 16.

[b] Includes patients who received a risankizumab dose at weeks 0, 4, and 16 and were withdrawn from risankizumab therapy afterward (patients were re-randomized to placebo in Part B). In Part B, some patients were re-treated with risankizumab after placebo withdrawal. These patients received risankizumab 150 mg SC at weeks 0, 4, and 16 or at week 0, and only after initiation of re-treatment with risankizumab.

[c] Includes all available interim data until week 104.

Source: UltIMMA-1,[20] UltIMMA-2,[21] and IMMhance,[22] IMMvent[23] Clinical Study Reports.

Discussion

Summary of Available Evidence

A total of four phase III RCTs were included in the CDR systematic review. UltIMMA-1 (N = 506) and UltIMMA-2 (N = 491) were identically designed multi-centre, randomized, double-blind, double-dummy, placebo-controlled, active comparator–controlled studies of risankizumab versus placebo and ustekinumab. IMMhance (N = 507) was a multi-centre, randomized, double-blind, placebo-controlled study of risankizumab versus placebo that is currently ongoing. IMMvent (N = 605) was a multi-centre, randomized, double-blind, double-dummy, active-controlled study designed to assess the efficacy and safety of risankizumab versus adalimumab. All four trials had similar inclusion and exclusion criteria and enrolled patients with moderate to severe plaque psoriasis, defined as BSA involvement of ≥ 10%, PASI ≥ 12, and sPGA ≥ 3, which is aligned with definitions of disease severity used in clinical trials in the Canadian Guidelines for the Management of Plaque Psoriasis.[6] In each study, patients were randomized to double-blind treatment in blocks and stratified by body weight (≤ 100 kg versus > 100 kg) and prior exposure to TNF antagonists. All four trials were conducted in two parts (A and B); co-primary end points (PASI 90 and sPGA clear or almost clear at week 16) were identical in the first part across trials. The methodology and objectives for Part B varied across studies.

One key limitation associated with each of the four trials is generalizability of the study population to Canadian patients with moderate to severe plaque psoriasis. Each of the reviewed trials included a number of exclusion criteria that limits the generalizability of the results, including patients with current or a history of malignant disease, and chronic or relevant acute infections such as active or latent tuberculosis, HIV, hepatitis C, or hepatitis B. Also of note is that in the study population across trials, previous exposure to traditional systemic treatment was substantially lower than observed in Canada by clinical expert consulted for this review. However, despite these limitations, according to the clinical expert consulted for this review, baseline characteristics of the study populations reflect a patient population with moderate to severe plaque psoriasis that is consistent with what would be seen in Canadian clinical practice. Another key limitation identified was the duration of the trials. Although a 16-week period is adequate to determine patient response, given that psoriasis is a chronic condition requiring lifelong treatment, the 52-week trial duration is insufficient to determine whether risankizumab will be efficacious and safe over the long term. Interim results from the ongoing single-arm, open-label extension study M15-997 were available for this review (summarized in Appendix 6); however, at the time of data cut-off, most patients had received only a single dose of risankizumab since entering the trial and efficacy results for all risankizumab-treated patients were not yet available. Thus, more long-term data are required to understand the prolonged efficacy and safety of risankizumab for moderate to severe plaque psoriasis.

Interpretation of Results

Efficacy

HRQoL was a key efficacy outcome identified in the CDR review protocol that was also identified as important to patients based on the patient input received. In all four included trials, HRQoL was measured using the validated, dermatology-specific DLQI instrument, which evaluates various aspects of a patient's daily life that may be affected by psoriasis

symptoms, including symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment, as detailed in Appendix 5.

Overall, treatment with risankizumab resulted in an improved HRQoL at 16 weeks after administration of the induction regimen in each of the four trials. A statistically significantly larger proportion of patients achieved a DLQI score of 0 or 1 at week 16 in the risankizumab group compared with the placebo and ustekinumab groups in UltIMMA-1 and UltIMMA-2 and compared with the placebo group in IMMhance. Similar results were observed in IMMvent, but this outcome was not included, as a ranked secondary end point and was not controlled for multiplicity. Although risankizumab appeared to continue to maintain improved HRQoL over ustekinumab in Part B of UltIMMA-1 and UltIMMA-2, the DLQI score in Part B was not included in the statistical hierarchy for any of the trials included in this CDR review; therefore, these results must be interpreted with consideration of type I error. The proportion of patients who achieved a DLQI score of 0 or 1 at week 44 was similar between the risankizumab and adalimumab groups during Part B of IMMvent.

The recognized estimates of the MCID for the DLQI range from 2.2 to 6.9.[18,19] Change from baseline in DLQI at week 16 was greater than 6.9 for all risankizumab groups in each of the four trials. The between-group difference in change from baseline compared with the change observed for ustekinumab in UltIMMA-1 and UltIIMMA-2 and compared with adalimumab in IMMvent ranged from −1.6 to −2.1. Similar results were observed at week 52 in terms of change from baseline DLQI in UltIMMA-1 and UltIMMA-2; in each of these studies, improvements observed at the end of week 16 were maintained through week 52 in both the ustekinumab and risankizumab groups, with the difference between risankizumab and ustekinumab ranging from −1.7 to 2.5. In IMMvent, a statistically significant difference was observed in favour of risankizumab compared with adalimumab at week 44. The between-group treatment difference was −3.9 at the end of Part B in IMMvent. When interpreting these results, it is important to consider that change from baseline in DLQI was not considered part of the statistical testing hierarchy in any of the studies included in this review. Further, the clinical benefit associated with the between-group difference in change from baseline DLQI at the end of parts A and B remains uncertain. In summary, the longer-term improvements in HRQoL with risankizumab versus other biologic treatments for plaque psoriasis remain uncertain.

Another efficacy outcome identified in the CDR review protocol and identified as important by patient groups was skin clearance, which was measured by PASI response and sPGA in the trials included in this review. The PASI is the most widely used instrument in psoriasis trials and is considered reliable using test–retest data and internal consistency; however, inter-rater reliability is poor due to variability. The sPGA is validated, reliable, and easy to use, but it cannot measure the extent of psoriasis and may not be sensitive to small changes in disease severity. PASI 90 and sPGA clear or almost clear at week 16 were the co-primary outcome measures in all of the trials included in this review. The magnitude of the treatment effect for both measures of skin clearance was approximately 20% in favour of risankizumab over the active comparator in each of the trials included in this review. According to the clinical expert consulted for this review, this difference over comparator drugs is clinically meaningful and, in clinical practice, a difference of 5% to 10% would be considered meaningful. However, there is no direct evidence to demonstrate the comparative efficacy and safety of risankizumab when used with IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) and the IL-23 inhibitor guselkumab. Further, in Canadian clinical practice, physicians may increase the dose of biologic treatment in patients whose condition has responded inadequately; therefore, the magnitude of the

treatment difference observed in the clinical trials of risankizumab may be lower in clinical practice in Canada. However, this may be less relevant for drugs covered by public plans, as strict reimbursement criteria pertaining to recommended dosage strength and frequency may limit the dosing regimen employed by physicians.

Treatment with risankizumab resulted in an improved PASI response after the administration of the induction regimen in each of the four trials. A statistically significantly larger proportion of patients achieved PASI 90 at week 16 in the risankizumab group compared with: the placebo and ustekinumab groups in UltIMMA-1and UltIMMA-2, the placebo group in IMMhance, and the adalimumab group in IMMvent. Similar results for the proportion of patients achieving PASI 100 at week 16 were observed in each trial. The proportion of patients who achieved PASI 90 and PASI 100 at week 52 was statistically significantly greater in patients who continued treatment with risankizumab versus ustekinumab in both the UltIMMA-1 and UltIMMA-2 trials. In IMMvent, switching to risankizumab was superior to continuing on adalimumab in the re-randomized patient population (ITT_B_RR) in terms of achieving PASI 90. Overall, risankizumab was superior to treatment with placebo and the active comparators (ustekinumab or adalimumab) after the induction regimen at week 16, after continued treatment at week 52, and after 28 weeks of treatment in inadequate responders to adalimumab.

Treatment with risankizumab was superior to placebo and the active comparator treatment (ustekinumab or adalimumab) in terms of sPGA in all trials included in this CDR review. A statistically significantly larger proportion of patients achieved sPGA clear or almost clear and sPGA clear at week 16 in the risankizumab group compared with the ustekinumab group in UltIMMA-1 and UltIMMA-2, and the adalimumab group in IMMvent. In Part B of UltIMMA-1 and UltIMMA-2, the proportion of patients who achieved sPGA clear and sPGA clear or almost clear at week 52 was statistically significantly greater in patients who continued treatment with risankizumab compared with ustekinumab; however, sPGA clear or almost clear at week 52 was not a ranked secondary end point and not controlled for multiplicity. In IMMvent, in the re-randomized population, a higher proportion of patients re-randomized to risankizumab than adalimumab achieved sPGA clear or almost clear and sPGA clear at week 44, but sPGA outcomes were not included in the ranked hierarchy for the statistical analysis and were not controlled for multiplicity. When considered as a whole and given the magnitude of the treatment difference, results of the four trials included in this review demonstrate that risankizumab offers a benefit over treatment with ustekinumab, adalimumab, and placebo for sPGA for at least up to 52 weeks for ustekinumab and 44 weeks for adalimumab.

All four trials included in this review took into account the potential impact of body weight and prior exposure to TNF antagonists on treatment response. Randomization was stratified based on body weight (≤ 100 kg versus > 100 kg) and prior TNF antagonist treatment, and the stratified analysis was conducted on the co-primary end points. Results of this analysis were generally similar to those observed in the full ITT population in each of the four trials in that risankizumab was superior to ustekinumab or adalimumab for PASI 90 and sPGA clear or almost clear, with the exceptions previously noted. Where differences from the primary analysis were identified, they were not consistent across studies and no clear pattern emerged. Thus, the effect of body weight (≤ 100 kg versus > 100 kg) or prior exposure to TNF antagonists on potential differences in response to treatment with risankizumab compared with ustekinumab or adalimumab remains unclear. Additional subgroup analyses conducted in the trials and of relevance to this review included disease severity (including patients with a PASI score above or below the median of each study,

sPGA 3, and sPGA 4), and history of psoriasis therapy (including those with and without previous exposure to non-biologic systemic therapy, and those with and without previous exposure to any biologic therapy). Although these subgroups analyses may lack statistical power, the treatment effects are aligned with those of the general study population in that the proportion of patients who achieved the co-primary end points were consistently higher in patients treated with risankizumab than in patients treated with placebo and are unlikely to represent concern. Overall, the results of the subgroup analyses do not identify any particular subgroup of patients that would respond differently to treatment with risankizumab.

Although results from Part B of the IMMhance study are of limited relevance to this review, the clinical expert consulted for this review acknowledged that evaluating patient response to treatment interruption is of clinical interest. The objective of Part B in the IMMhance study was to compare the efficacy of continued treatment with risankizumab versus withdrawal from the treatment (ITT_B_R population). The key efficacy end point of Part B was the proportion of patients in the ITT_B_R population who achieved sPGA clear or almost clear at week 52. Although a statistically significantly higher proportion of patients in the ITT_B_R population who continued risankizumab achieved sPGA clear or almost clear at week 52, the response was maintained in approximately 60% of patients who switched to placebo. In addition, just more than half of the patients who switched to placebo achieved PASI 90 at week 52, although the proportion was still higher in the group of patients who continued risankizumab (but this outcome was not controlled for multiplicity). The implications of these results have yet to be determined.

Finally, outcomes relating to patient-reported symptoms were identified in the CDR review protocol. The PSS is a patient-reported instrument that assesses the severity of psoriasis symptoms, but no evidence of its validity and reliability was identified. In Part A of UltIMMA-1 and UltIMMA-2, a statistically significantly higher proportion of patients achieved a PSS of 0 at week 16 in the risankizumab group over placebo groups. While similar results were observed for risankizumab compared with patients treated with ustekinumab in Part A, the comparison between the risankizumab and ustekinumab groups was not included in the statistical analysis hierarchy in either study. The proportion of patients who achieved a PSS score of 0 in Part B was also higher in patients treated with risankizumab than those treated with ustekinumab, but was outside the statistical testing hierarchy for both studies and was not controlled for multiplicity. Thus, whether risankizumab offers any benefit on the patient-reported symptoms compared with other biologic treatments for plaque psoriasis remains uncertain.

Overall, data are consistent across the four trials of risankizumab and the magnitude of the difference between risankizumab and ustekinumab and adalimumab was large for each of the outcomes measured in UltIMMA-1, UltIMMA-2, and IMMvent. Further, according to the clinical expert consulted for this review, the results observed with ustekinumab in UltIMMA-1 and UltIMMA-2 are consistent with the response typically observed in clinical practice.

The currently available biologic drugs are appropriate for long-term use and are generally associated with evidence of disease clearance within three months of initiating treatment.[2] It is estimated that approximately 20% of patients will discontinue treatment with a biologic;[31-36] however, according to the clinical expert consulted for this review, discontinuation rates are lower in Canada due to the clinical practice of increasing the dose of the current biologic in patients who do not exhibit an adequate response. Risankizumab is one of nine

biologics that may be tried when another drug fails or is not appropriate. Results from Part B of the IMMvent study are of particular relevance to clinical practice, as they specifically demonstrate the efficacy of risankizumab in a population of patients with an inadequate response to adalimumab. Although the treatment administration protocol may not be completely aligned with clinical practice in that no dose increase of adalimumab was tried before switching to risankizumab, the administration was aligned with the dosing recommended by Health Canada. Note that dose increases with adalimumab are beyond the dosing recommended by Health Canada. However, current Canadian psoriasis guidelines do not mention increasing the dose of adalimumab in patients who do not respond to the drug.[5]

Harms

In general, risankizumab appeared to be well tolerated based on the harms data reported in the four included trials. The proportion of patients experiencing an AE was similar or slightly lower in the risankizumab group versus the ustekinumab group in Part A and Part B of UltIMMA-1 and UltIMMA-2 and similar to placebo in both trials. The most frequently reported AEs were upper respiratory tract infection and viral respiratory tract infection in UltIMMA-1, and diarrhea, nausea, back pain, and headache in UltIMMA-2, all of which were more common in the ustekinumab group than in the risankizumab group; arthralgia was more common in the risankizumab group in UltIMMA-2. In general, the AE profile was similar between the risankizumab and ustekinumab groups. In IMMhance, AEs occurred in a similar proportion of patients in the risankizumab and placebo groups from week 0 to 16. The most frequently reported AEs during the study were upper respiratory tract infection and viral upper respiratory tract infection; arthralgia was also commonly reported during Part B. In IMMvent, AEs occurred in a similar proportion of patients in the risankizumab and adalimumab groups. The most frequently reported AEs were upper respiratory tract infection and viral respiratory tract infection, which were more common in the risankizumab group than in the adalimumab group. Of note, a higher proportion of patients re-randomized to risankizumab in Part B of IMMvent reported viral upper respiratory tract infection than those re-randomized to adalimumab (26.4% versus 12.5%, respectively). Further, the proportion of risankizumab-treated patients who reported viral upper respiratory tract infection was higher in Part B of IMMvent (26.4%) than across all parts of UltIMMA-1 (16.1%) and UltIMMA-2 (13.9%). The reason for this discrepancy across trials is unknown. Headache occurred in a higher proportion of patients in the adalimumab group than in the risankizumab group. In part B in the Safety B_RR population, AEs were reported in a higher proportion of patients re-randomized to risankizumab than in patients re-randomized to adalimumab; the safety profile for Part B was similar to that described for Part A.

SAEs occurred infrequently regardless of the treatment period and treatment group in all four included trials. No SAE was observed in more than two patients in any study. The rate of withdrawals due to AEs was low (< 2.5%, with the exception of patients re-randomized to adalimumab in IMMvent at 3.6%) in all safety analysis populations across all studies and was well balanced across treatment groups in both Part A and Part B. Treatment with risankizumab did not appear to be associated with increased mortality, as there were only seven deaths reported across the four included trials (i.e., two deaths each in UltIMMA-2 and IMMhance, and three deaths in IMMvent), with no deaths reported in UltIMMA-1.

Other biologic treatments are associated with infections, MACE (TNF-alpha inhibitors), and inflammatory bowel disease (IL-17 inhibitors), and brodalumab has been associated with suicidal ideation and behaviours.

In general, the rate of infections was low in each of the trials. Overall, the frequency of serious infection varied across trials and between treatment groups, but fungal infections were [redacted]. None of the fungal infections were considered to be SAEs.

In the current review, the proportion of patients experiencing injection-site reactions was [redacted].

In UltIMMA-1 and UltIMMA-2, a [redacted].

In UltIMMA-1 and UltIMMA-2, the incidence of anti-drug antibodies and NAb was [redacted]. In IMMhance, the incidence of treatment-emergent anti-drug antibodies and NAb was [redacted] in patients who were treated with risankizumab throughout the study and those who were switched from placebo to risankizumab (placebo group) or from risankizumab to placebo (placebo withdrawal). In IMMvent, the incidence of treatment-emergent anti-drug antibodies and NAb was [redacted] in patients who were treated with risankizumab throughout the study and those who were switched from adalimumab to risankizumab.

In general, the frequency of MACE was low in each of the trials included in this review. The incidence of inflammatory bowel disease was not reported in any of the studies, and no clear pattern of psychiatric symptoms emerged with risankizumab during UltIMMA-1, UltIMMA-2, IMMhance, or IMMvent.

Safety outcomes were reported in the ITC submitted by the manufacturer, which showed that over the short-term induction-treatment period (10 or 16 weeks), risankizumab had significantly lower odds of AEs when compared with dimethyl fumarate, infliximab, secukinumab, ixekizumab, and brodalumab, and that risankizumab was associated with significantly lower odds of discontinuation due to AEs compared with placebo, apremilast 30 mg, adalimumab 80 mg, dimethyl fumarate, infliximab 5 mg/kg, ixekizumab 160 mg, brodalumab 210 mg, and guselkumab 100 mg. No significant difference between risankizumab and other interventions in terms of SAEs was observed.

It should be noted that there may not be sufficient data to identify rare or latent AEs that may be associated with prolonged risankizumab use. An open-label extension trial (M15-997) to evaluate the safety of risankizumab up to week 156 is currently ongoing; however, the data available from the interim analysis available at the time of this review are limited to a subset of patients who switched to risankizumab, and most patients had received only a

single dose of risankizumab during the open-label extension. Study M15-997 is described in further detail in Appendix 6.

The main evidence gaps include the absence of direct evidence demonstrating the comparative efficacy and safety of risankizumab with IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) and the IL-23 inhibitor guselkumab and long-term data. Results of the two ITCs appraised in this CDR review suggest that over short-term induction-treatment periods (ranging from 10 to 16 weeks), the relative risk of achieving PASI 75 and PASI 90 responses is significantly greater for risankizumab than for placebo, apremilast, etanercept, adalimumab, ustekinumab, infliximab, and secukinumab in patients with moderate to severe chronic plaque psoriasis; no significant differences for risankizumab versus ixekizumab, brodalumab, or guselkumab were observed. [redacted]. Neither of these ITCs included outcome measures beyond the short-term induction period; therefore, there is uncertainty pertaining to the additional efficacy and safety benefit that risankizumab may have compared with long-term use of these newer biologic treatments.

Potential Place in Therapy[2]

The clinical expert consulted by CADTH noted that there are nine biologics (including risankizumab) approved for the treatment of moderate to severe plaque psoriasis in Canada. Risankizumab is one of two anti–IL-23 drugs; the other one is guselkumab.

Biologics are currently used as continuous therapy. The clinical expert indicated that when a patient is started on a biologic, the treatment is expected to be continuous and lifelong. A major unmet need is a treatment that is remittive or would work well on an intermittent "as-needed" basis. So far, risankizumab and other biologics do not have clinical trial evidence in this regard and are not positioned in clinical practice to fulfill this need.

Risankizumab appears to be more efficacious than adalimumab and ustekinumab, based on the reviewed trials. The efficacy and safety profile of risankizumab seems similar to the other anti–IL-23 drug, guselkumab, but lacks head-to-head data. Risankizumab may be more convenient for patients, as it requires fewer injections (every 12 weeks versus every 8 weeks) compared with guselkumab. Risankizumab provides another choice for patients and physicians.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

Overall, the four trials included in this review support risankizumab as an efficacious treatment with a safety profile at least similar to other biologics used for patients with moderate to severe plaque psoriasis. Three studies included active comparators to risankizumab: two were versus ustekinumab (UltIMMA-1 and UltIMMA-2) and one was versus adalimumab (IMMvent). Overall, risankizumab demonstrated superior benefit after administration of the induction regimen to ustekinumab and adalimumab in terms of HRQoL and in skin clearance measures of PASI 90 and sPGA at week 16. As shown in UltIMMA-1 and UltIMMA-2, the benefit of risankizumab over ustekinumab for PASI 90 and sPGA was maintained up to week 52. Further, in patients who did not exhibit an adequate response to adalimumab, a higher proportion achieved PASI 90 after switching to risankizumab for 28 weeks compared with continuing adalimumab, as demonstrated in the IMMvent study. The included trials generally appear to have been performed with methodological rigour with a low risk of bias, and included a trial population that was reflective of patient characteristics and treatments typical of the Canadian context.

Other biologic treatments are associated with inflammatory bowel disease or psychiatric symptoms, and no such AEs were identified in the clinical trials of risankizumab included in this review. Treatment with risankizumab did not appear to be associated with an increased incidence of injection-site reactions or MACE [redacted].

There is no direct evidence comparing risankizumab with IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) or the IL-23 inhibitor guselkumab. Results of the two ITCs appraised in this CDR review suggest that over short-term induction-treatment periods (ranging from 10 to 16 weeks), the relative risk of achieving PASI 75 and PASI 90 responses is significantly greater for risankizumab than for placebo, apremilast, etanercept, adalimumab, ustekinumab, infliximab, and secukinumab in patients with moderate to severe chronic plaque psoriasis; no significant differences for risankizumab versus ixekizumab, brodalumab, or guselkumab, were observed. [redacted]. There is uncertainty pertaining to the additional efficacy and safety benefit that long-term treatment with risankizumab may have over these newer biologic treatments.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient input submissions were received: one from Arthritis Consumer Experts (ACE) and one from the Canadian Psoriasis Network (CPN) in collaboration with the Canadian Skin Patient Alliance (CSPA) and the Canadian Association of Psoriasis Patients (CAPP).

ACE is a national, non-profit, organization in Canada serving people living with all forms of arthritis. The organization provides free, science-based information and education programs to people with arthritis and advocates on health and policy issues related to arthritis through ACE's JointHealth programs and the Arthritis Broadcast Network. ACE declared no conflicts of interest.

CPN, CSPA, and CAPP (a partner organization of CSPA) are national, non-profit organizations. CPN works to improve the quality of life of Canadians with psoriasis and psoriatic arthritis. CSPA provides advocacy, education, and support for Canadians with skin diseases, conditions, and traumas. CAPP serves the needs of patients with psoriasis across Canada. CPN, CSPA, and CAPP declared financial payment over the past two years from various pharmaceutical manufacturers, including AbbVie Canada, the manufacturer of risankizumab.

2. Condition-Related Information

ACE issued a call for input on September 27, 2018 from patients with psoriatic arthritis and plaque psoriasis. Information was also gathered from day-to-day interactions with people living with plaque psoriasis, work with clinical researchers in Canada, and discussions with consumers, patients, and scientific members of the ACE Advisory Board. Information for this submission was gathered from January to November 2018.

CPN, CSPA, and CAPP gathered information through a patient survey administered in English from August 26 to September 20, 2018 through Survey Monkey. Nineteen responses were received from British Columbia, Alberta, Ontario, and New Brunswick. This submission was also supplemented by data from a questionnaire issued by CPN/CAPP that explored the meaning of disease stability among 286 people with psoriasis.

Plaque psoriasis is a chronic inflammatory skin condition that is characterized by periods of remission and flares. During flares, patients report symptoms of itchiness, pain, skin sensitivity, redness, and skin that cracks and bleeds. Plaque psoriasis most commonly affects the elbows, knees, and scalp, but other areas such as the palms of hands, soles of feet, nails, genitals, and torso may also be involved. Several patients mentioned the presence of skin flakes that appear everywhere, and this causes considerable distress. Plaque psoriasis ranges in severity, from nuisance to disabling condition. For example, patients reported that "Life is difficult with this disease . . . it's so painful . . ." and "My well-being is . . . just not well." Patients are in constant consideration of the state of their disease and may experience difficulty with daily activities, such as showering and cooking. Due to limited time and energy and embarrassment associated with their skin's appearance, the disease may cause restrictions in social and creative activities and travel and affect choice of clothing. Patients stated, "I was unable to participate in any social activity, could not walk down stairs and did not feel like socializing due to the pain and discomfort . . ."; "I will not travel to tropical destinations or beaches"; and "I don't want to go swimming or to the

beach, and that affects my family." In the CPN/CAPP questionnaire, many patients (74%) perceived that their condition was uncontrolled and more than 38% had lived for 10 or more years feeling that their condition was not satisfactorily controlled.

In addition to the physical symptoms of plaque psoriasis, patients reported impacts on their mental and emotional health. Feelings of frustration, worry, embarrassment, anxiety, and depression were commonly mentioned. In the CPN/CAPP patient survey, one-third of participants indicated loss of sleep, negative effects on self-confidence, and problems with intimacy. Forty-seven per cent indicated their concentration at work was frequently affected. One patient mentioned that other people were concerned that her disease was contagious and "used to clear the beach — people would look at us and would clear out."

The impact on caregivers is also significant with respect to the time required to help patients manage their disease and disease-related chores, as well as the emotional burden, lack of support or information, and missing school, work, and social events.

3. Current Therapy Related Information

In the submission from ACE, one patient mentioned that treatment (medication name not specified) improved plaque psoriasis on the scalp and reduced itchiness, although side effects included heartburn and dizziness. Taking a combination of etanercept plus methotrexate helped a patient to control psoriasis and reduced joint inflammation, but caused gastrointestinal upset and mucus-membrane irritation, which were manageable with folic acid.

In the CPN/CSPA/CAPP survey, patients reported the use of different treatment modalities, including topical, phototherapy, and oral systemic medications and biologics. Just less than 54% indicated that therapies were somewhat effective for reducing plaques and spots and 15% indicated that therapies were very effective. Just more than 41% indicated therapies were somewhat effective in addressing pain and 25% indicated that therapies were very effective. Forty-six per cent indicated that therapies were somewhat effective in addressing redness and shedding and 15% indicated that therapies were very effective. The majority (58%) said that the medications were very convenient to use.

Some patients mentioned that despite treatment, they still experienced new outbreaks and the therapies provided only temporary solutions. For one patient, topical treatments plus phototherapy worked for many years for plaque psoriasis on the body, but not on the soles of feet or hands; the patient eventually saw results with adalimumab. Other patients mentioned that treatments were not producing any effect at all or had side effects.

The side effects of treatments included tiredness, extreme dryness of face and lips, redness, soreness, thinning skin, painful burns, hair loss, and weight gain. In the input submitted by ACE, patients were concerned about the side effects associated with long-term use of currently available treatments and desired an effective treatment with the lowest risk of side effects.

Patients were also concerned about access and affordability of treatments (e.g., the biologics) for plaque psoriasis. They would like to have more options available that adequately control or stop symptoms such as itchiness, scaling, pain, bleeding, and flaking without side effects. Treatment responses vary among patients and what works for one may not work for another, even when the symptoms are similar. Therefore, the availability of more treatment options would provide patients with choices to manage the disease.

4. Expectations About the Drug Being Reviewed

No patients in the ACE input provided experiences with or expectations of risankizumab.

CPN conducted four telephone interviews with patients who had participated in a clinical trial for risankizumab. A clinical research coordinator with the SkiN Centre for Dermatology identified these patients and obtained their verbal consent for a telephone interview by CPN about their experience with the medication. The four patients had all experienced inadequate responses with a range of previous treatments. Patients mentioned that risankizumab was convenient to use, with administration every three to four months. Treatment responses were reported, such as almost-clear skin, not itchy all the time, and not as self-conscious about participating in activities; skin clearance was the most notable response. In addition, all of the patients reported that they did not have any side effects. Patients mentioned they had had additional monitoring by family doctors while on the medication, although this was not viewed as an obstacle to treatment.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 16, 2018
Alerts:	Bi-weekly search updates until March 20, 2019.
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm	Name of substance word
.pt	Publication type
.mp	Mapped term
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(risankizumab or Skyrizi or 655066-01 or “65506601” or BI-655066 or BI655066 or ABBV-066 or ABBV066 or 90ZX3Q3FR7).ti,ab,ot,kf,hw,rn,nm.
2	1 use medall
3	*risankizumab/
4	(risankizumab or Skyrizi or 655066-01 or BI-655066 or BI655066 or ABBV-066 or ABBV066).ti,ab,kw,dq
5	or/3-4
6	5 use oemezd
7	6 not (conference review or conference abstract).pt.

MULTI-DATABASE STRATEGY	
8	2 or 7
9	remove duplicates from 8

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (ClinicalTrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 2018
Keywords:	Skyrizi (risankizumab), psoriasis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Table 21: Excluded Studies

Reference	Reason for Exclusion
Clinical Study Report: M15-997. A multicenter, open-label study to assess the safety and efficacy of risankizumab for maintenance in moderate to severe plaque type psoriasis [CONFIDENTIAL internal manufacturer's report]. Chicago (IL): AbbVie Inc.; 2018 Jan 8.	Not an RCT; does not meet inclusion criteria in the CDR protocol
Fioranelli M, Roccia mg, Lotti T. Risankizumab versus ustekinumab for moderate to severe plaque psoriasis. *Dermatol Ther.* 2017;30(5):09.	Letter to the editor; Not an RCT; does not meet inclusion criteria in the CDR protocol
Kolli SS, Gabros SD, Pona A, Cline A, Feldman SR. Tildrakizumab: A Review of Phase II and III Clinical Trials. *Ann Pharmacother.* 2018:1060028018809522.	Systematic review; does not meet inclusion criteria in the CDR protocol
Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate to severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* 2015;136(1):116-124.e117.	Phase I trial; does not meet inclusion criteria in the CDR protocol
Lee EB, Amin M, Bhutani T, Wu JJ. Emerging therapies in psoriasis: a systematic review. *Cutis.* 2018;101(3S):59.	Systematic review; does not meet inclusion criteria in the CDR protocol
Papp KA, Blauvelt A, Bukhalo M, et al. Risankizumab versus Ustekinumab for Moderate to Severe Plaque Psoriasis. *N Engl J Med.* 2017;376(16):1551-1560.	Phase II trial; not identified as pivotal; does not meet inclusion criteria in the CDR protocol

CDR = CADTH Common Drug Review; RCT = randomized controlled trial.

Appendix 4: Detailed Outcome Data

Table 22: Proportion of Patients Achieving a Psoriasis Area and Severity Index Score of 75 at Week 16 (Nonresponder Imputation; Intention-to-Treat Population)

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
	PBO (N = 102)	UST (N = 100)	RZB (N = 304)	PBO (N = 98)	UST (N = 99)	RZB (N = 294)	PBO (N = 100)	RZB (N = 407)	ADA (N = 304)	RZB (N = 301)
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8 (8.0)	361 (88.7)	218 (71.7)	273 (90.7)
Adjusted difference vs. RZB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	80.6 (74.5 to 86.6)	–	18.9 (13.0 to 24.9)	–
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	< 0.001	–	< 0.001	–

ADA = adalimumab; CI = confidence interval; IPBO = placebo; RZB = risankizumab; UST = ustekinumab; vs. = versus.

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Table 23: Primary Efficacy Outcomes at Week 16 — Stratified Subgroup Analysis

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
	PBO (N = 102)	UST (N = 100)	RZB (N = 304)	PBO (N = 98)	UST (N = 99)	RZB (N = 294)	PBO (N = 100)	RZB (N = 407)	ADA (N = 304)	RZB (N = 301)
Proportion of Patients Achieving PASI 90 at Week 16 (NRI)										
Baseline weight ≤ 100 kg and prior exposure to TNF antagonists = 0										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. RZB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline weight > 100 kg and prior exposure to TNF antagonists = 0										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. RZB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline weight ≤ 100 kg and prior exposure to TNF antagonists ≥ 1										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. RZB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline weight > 100 kg and prior exposure to TNF antagonists ≥ 1										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	UltIMMA-1			UltIMMA-2			IMMhance		IMMvent	
	PBO (N = 102)	UST (N = 100)	RZB (N = 304)	PBO (N = 98)	UST (N = 99)	RZB (N = 294)	PBO (N = 100)	RZB (N = 407)	ADA (N = 304)	RZB (N = 301)
n (%)										
Difference vs. RZB (95% CI)										
P value										
Proportion of Patients Achieving an sPGA Score of 0 or 1 (Clear or Almost Clear) at Week 16 (NRI)										
Baseline weight ≤ 100 kg and prior exposure to TNF antagonists = 0										
N										
n (%)										
Difference vs. RZB (95% CI)										
P value										
Baseline weight > 100 kg and prior exposure to TNF antagonists = 0										
N										
n (%)										
Difference vs. RZB (95% CI)										
P value										
Baseline weight ≤ 100 kg and prior exposure to TNF antagonists ≥ 1										
N										
n (%)										
Difference vs. RZB (95% CI)										
P value										
Baseline weight > 100 kg and prior exposure to TNF antagonists ≥ 1										
N										
n (%)										
Difference vs. RZB (95% CI)										
P value										

ADA = adalimumab; CI = confidence interval; NRI = nonresponder; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab; sPGA = static Physician Global Assessment; TNF = tumour necrosis factor; UST = ustekinumab; vs. = versus.

[a] For Part A, CI and *P* values are computed for comparison between RZB versus UST, and RZB versus PBO. Within each stratum, the 95% CI for the difference was calculated based on normal approximation to the binomial distribution.

[b] Within each stratum, the *P* value was calculated based on chi-square test (or Fisher's exact test if ≥ 25% of the cells had an expected cell count of < 5).

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Table 24: Primary Efficacy Outcomes at Week 16 — Subgroup Analysis

	UltIMMA-1		UltIMMA-2		IMMhance		IMMvent	
	PBO (N = 102)	RZB (N = 304)	PBO (N = 98)	RZB (N = 294)	PBO (N = 100)	RZB (N = 407)	ADA (N = 304)	RZB (N = 301)
Proportion of Patients with PASI 90 at Week 16, n/N (%)								
Baseline PASI score ≤ median[a]	[redacted]							
Baseline PASI score > median[a]								
Baseline sPGA of 3								
Baseline sPGA of 4								
Prior exposure to non-biologic systemic treatment								
No prior exposure to non-biologic systemic treatment								
Prior exposure to biologics								
No prior exposure to biologics								
Proportion of Patients With sPGA Clear or Almost Clear (0 or 1) at Week 16, n/N (%)								
Baseline PASI score ≤ median[a]								
Baseline PASI score > median[a]								
Baseline sPGA of 3								
Baseline sPGA of 4								
Prior exposure to non-biologic systemic treatment								
No prior exposure to non-biologic systemic treatment								
Prior								

	UltIMMA-1		UltIMMA-2		IMMhance		IMMvent	
	PBO (N = 102)	RZB (N = 304)	PBO (N = 98)	RZB (N = 294)	PBO (N = 100)	RZB (N = 407)	ADA (N = 304)	RZB (N = 301)
exposure to biologics				[redacted]		[redacted]		
No prior exposure to biologics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab; sPGA = static Physician Global Assessment.

[a] The median baseline PASI score was 18.35 in UltIMMA-1, 17.5 in UltIMMA-2 and IMMhance, and 17.70 in IMMvent.

Source: UltIMMA-1,[20] UltIMMA-2,[21] IMMhance,[22] and IMMvent[23] Clinical Study Reports.

Table 25: Key Efficacy Outcomes at Week 52 — IMMhance (ITT_B_R Population)

	ITT_B_R Population		ITT_B_PBO_RT Population
	RZB/RZB/PBO (N = 225)	RZB/RZB/RZB (N = 111)	RZB/RZB/PBO/RZB (N = 40)
Proportion of Patients Achieving PASI 90 (NRI)			
Week	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]
Adjusted difference (95% CI)	[redacted]		[redacted]
P value	[redacted]		[redacted]
Proportion of Patients Achieving PASI 100 (NRI)			
Week	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]
Adjusted difference (95% CI)	[redacted]		[redacted]
P value	[redacted]		[redacted]
Proportion of Patients Achieving an sPGA Score of 0 or 1 (Clear or Almost Clear) (NRI)			
Week	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]
Adjusted difference (95% CI)	[redacted]		[redacted]
P value	[redacted]		[redacted]
Proportion of Patients Achieving an sPGA Score of 0 (Clear) (NRI)			
Week	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]
Adjusted difference (95% CI)	[redacted]		[redacted]
P value	[redacted]		[redacted]

CI = confidence interval; ITT = intention-to-treat; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; RZB = risankizumab; sPGA = static Physician Global Assessment; vs. = versus.

Source: IMMhance Clinical Study Report.[22]

Table 26: Key Efficacy Outcomes at Week 44 — IMMvent (Nonresponder Imputation)

	ADA/ADA (ITT_B_R Population) (N = 144)	ADA/RZB (ITT_B_NR population) (N = 38)	RZB/RZB (ITT_B_RZB Population) (N = 301)
Proportion of patients achieving a DLQI score of 0 or 1, n (%)	[redacted]	[redacted]	[redacted]
DLQI Change From Baseline to Week 44 (LOCF)			
N	[redacted]	[redacted]	[redacted]
Baseline, mean	[redacted]	[redacted]	[redacted]
Week 44, mean	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]
Proportion of patients achieving PASI 90, n (%)	[redacted]	[redacted]	[redacted]
Proportion of patients achieving PASI 100, n (%)	[redacted]	[redacted]	[redacted]
Proportion of patients achieving an sPGA score of 0 or 1 (clear or almost clear), n (%)	[redacted]	[redacted]	[redacted]
Proportion of patients achieving an sPGA score of 0 (clear), n (%)	[redacted]	[redacted]	[redacted]

ADA = adalimumab; DLQI = Dermatology Life Quality Index; ITT = intention-to-treat; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index; RZB = risankizumab; SE = standard error; sPGA = static Physician Global Assessment.

Source: IMMvent Clinical Study Report.[23]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Psoriasis Area and Severity Index (PASI)
- static Physician's Global Assessment (sPGA)
- Dermatology Life Quality Index (DLQI)
- Psoriasis Symptoms Scale (PSS).

Findings

Table 27: Brief Descriptions of Instruments Used in the Trials

Instrument	Type	Evidence of Validity	MCID/Benchmark	References
PASI	A single estimate of a patient's disease severity at a given time based on induration, erythema, and scaling.	YES	PASI 90 and PASI 100 are the updated treatment goals in clinical practice. PASI 75 is a traditional outcome, although it may still be clinically meaningful to patients. MCID for PASI scores were not identified.	Ashcroft et al. (1999)[43] Carlin et al. (2004)[41] Feldman et al. (2004)[44] Gourraud et al. (2012)[45] Mattei et al. (2014)[46]
sPGA	The sPGA is used to determine a single estimate of the patient's overall severity of disease at a given point in time. Psoriatic lesions are graded for induration, erythema, and scaling based on scales of 0 to 5 that are then averaged over all lesions.	YES	Not identified.	Weisman et al. (2003)[47] Cappelleri et al. (2013)[48] Chow et al. (2015)[49] Simpson et al. (2015)[50]
DLQI	A 10-item, dermatology-specific quality-of-life questionnaire.	YES	Range: 2.2 to 6.9.	Finlay et al. (1994)[40] Shikiar et al. (2003)[51] Mazzotti et al. (2003)[52] Shikiar et al. (2006)[18] Basra et al. (2008)[19]
PSS	A patient-reported outcome to assess severity of psoriasis symptoms. Symptoms of pain, redness, itching, and burning are rated on a 5-point Likert scale of 0 to 4. The PSS is based on the PSI and PSD.	NO The PSI and PSD have evidence of validity.	Not identified.	PSI: Bushnell et al. (2013)[53] Strober et al. (2016)[54] Viswanathan et al. (2017)[55] PSD: Strober et al. (2013)[56] Lebwohl et al. (2014)[57]

MCID = minimal clinically important difference; PASI = Psoriasis Area and Severity Index; PSD = Psoriasis Symptom Diary; PSI = Psoriasis Symptom Inventory; PSS = Psoriasis Symptoms Scale; sPGA = static Physician's Global Assessment.

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific health-related quality of life (HRQoL) instrument. It is a 10-item questionnaire that measures the effect of having skin disease on six different aspects relating to quality of life: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[18,40] Each of the 10 questions is given a score of 0, 1, 2, or 3 based on the following responses, respectively: "not at all," "a little," "a lot," or "very much." The maximum score per aspect is either 3 (with a single question) or 6 (with two questions) and the scores for each can be expressed as a percentage of either 3 or 6. The overall DLQI is calculated by summing the score of each question, resulting in a numeric score between 0 and 30 (or a percentage of 30).[18,40] The higher the score, the greater the degree of quality-of-life impairment. The meanings of the DLQI scores in terms of the effect on a patient's life are as follows:[19]

- 0 to 1 = no effect
- 2 to 5 = small effect
- 6 to 10 = moderate effect
- 11 to 20 = very large effect
- 21 to 30 = extremely large effect

The DLQI has shown good test–retest reliability based on reassessment seven to 10 days after the initial assessment (the correlation between overall DLQI scores was 0.99; $P < 0.0001$; for individual question scores, the correlation was 0.95 to 0.98; $P < 0.001$).[40] The DLQI has also shown good internal consistency reliability (with Cronbach's alpha coefficients ranging from 0.75 to 0.92 when assessed in 12 international studies),[19] construct validity (as 37 separate studies have mentioned correlation of the DLQI with either generic or dermatology-specific and disease-specific measures),[19] and responsiveness (the DLQI is reportedly able to detect changes over time, according to 17 different studies).[19] Similar measures of the validity, reliability, and responsiveness of the DLQI have also been shown in evaluations of the use of the instrument specifically for adult patients with moderate to severe psoriasis.[51,52]

Estimates of the minimal clinically important difference (MCID) — that is, the smallest difference a patient would regard as beneficial — have ranged from 2.2 to 6.9.[18,19] It should be noted that some of the anchors that were used to obtain the DLQI MCID were not patient-based (i.e., Basra et al.[19] derived estimates from PASI and Physician's Global Assessment anchors, as well as a distribution-based approach); therefore, they do not necessarily identify the smallest difference that patients would consider important.

Limitations associated with the DLQI are as follows:

- Concerns have been identified regarding unidimensionality and the behaviour of items of the DLQI in different patient populations with psoriasis with respect to their equivalence across different cultures, ages, and genders.[19]
- The patient's emotional aspects may be underrepresented; this may be one reason for unexpectedly low DLQI scores in patients with more emotionally disabling diseases, such as vitiligo. To overcome this, it is suggested that the DLQI be combined with more emotionally oriented measures, such as the mental component of the Medical Outcomes Study 36-Item Short Form Survey (SF-36) or the Hospital Anxiety and Depression Scale.[19]

- The DLQI may lack sensitivity in detecting a change from mild to severe psoriasis.[58]

Psoriasis Area and Severity Index

The PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. A PASI score of less than 10 is considered mild disease and a score of 10 or greater is considered moderate to severe disease.[59] A 75% reduction in the PASI score (PASI 75) was the traditional benchmark for clinical trials in psoriasis and was the criterion for the efficacy of new psoriasis treatments approved by the FDA.[41] However, according to a clinical expert consulted for this review, in current clinical practice, the treatment goal is achievement of PASI 90 or PASI 100.

The PASI is calculated by dividing the body into four regions: head (h), upper extremities (u), trunk (t), and lower extremities (l). These account for 10%, 20%, 30%, and 40% of the total body surface area (BSA), respectively.[44] Each of these areas is assessed separately for erythema, induration, and scaling, and rated on a scale of 0 (none) to four (very severe). The extent of psoriatic involvement for each region is graded as follows:

- 0 = no involvement
- 1 = 1% to 9%
- 2 = 10% to 29%
- 3 = 30% to 49%
- 4 = 50% to 69%
- 5 = 70% to 89%
- 6 = 90% to 100%

The following formula is used to calculate the PASI score:[44]

PASI = 0.1 (Eh + Ih + Sh) Ah + 0.2 (Eu + Iu + Su) Au + 0.3 (Et + It + St) At + 0.4 (El + Il + Sl) Al

(where E = erythema, I = induration, S = scaling, A = area, h = head score, t = trunk score, u = upper extremities score, and l = lower extremities score; PASI 90 or PASI 100 is scored using a dichotomous scale: Yes/No: patient achieved ≥ 90% or 100% improvement from baseline PASI score).

A number of limitations of the PASI have been identified:

- The PASI has been criticized for not correlating the clinical extent of the disease with HRQoL and the psychological stress caused by psoriasis. The patient's measure of quality of life is often worse than the physician-rated clinical severity.[60]
- There are significant inter-rater reliability issues regarding the measurement of BSA.[43,44] There has been some work regarding the development of imaging and analysis systems to objectively measure BSA.[61] PASI scores can vary substantially between experienced and inexperienced physicians, raising concerns for inter-rater reliability.[62]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[41,44] The extent of psoriatic involvement is measured using a scale of 1 to 6 and the areas corresponding to each score are non-linear.

- Some severe disease (clinically) may be scored low. For example, PASI scores as low as 3 (for palms and soles) may represent psoriasis that disables a patient from work and other life activities.
- Most patients fall into a narrow band of scores, thereby decreasing the usefulness of the full range of scores (i.e., scores higher than 40 are rare).[43] The validity of this scale may be overrated, in part because of the skew toward lower scores.[45]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[63]
- The PASI lacks sensitivity, as erythema, desquamation, and induration are scored with equal weight within each of the four body regions. Thus, a reduction in scaling with a concomitant increase in skin erythema could be recorded with the same PASI score.
- An improvement in the histological phenotype of psoriasis can be underestimated by the improvement percentage in the PASI score (e.g., reduction of T-cells, loss of K16 expression, and reduction in epidermal thickness).[41]

Static Physician's Global Assessment

The Physician's Global Assessment (PGA) is a measure used by physicians to determine the patient's overall severity of disease and is available in both a dynamic and a static form (sPGA). The former is an assessment of the change from baseline; the latter is measured at a single point in time.[42] Various PGAs have been used in psoriasis with different descriptions and scores.[62]

The static version was used by the trials in this review. In UltIMMA-1, UltIMMA-2, IMMvent, and IMMhance, sPGA was based on a composite score of a physician assessment of erythema, average thickness, and scaling of all psoriatic lesions. Each category was scored on a five-point scale (0 to 4), according to the following classification system:[20,21,23,64]

- Erythema
  - 0 = Normal (post-inflammatory hyper/hypopigmentation may be present)
  - 1 = Faint, diffuse pink, or slight red coloration
  - 2 = Mild (light red coloration)
  - 3 = Definite red coloration (Dull to bright red)
  - 4 = Bright to deep red coloration of lesions
- Induration (plaque elevation)
  - 0 = None
  - 1 = Just detectable (possible slight elevation above normal skin)
  - 2 = Mild thickening (slight but definite elevation, typically edges are indistinct or sloped)
  - 3 = Clearly distinguishable to moderate thickening (marked definite elevation with rough or sloped edges)
  - 4 = Severe thickening with hard edges (marked elevation typically with hard or sharp edges)
- Scaling
  - 0 = No scaling
  - 1 = Minimal focal scaling (surface dryness with some desquamation)
  - 2 = Predominately fine scaling (fine scale partially or mostly covering lesions)

- 3 = Moderate scaling (coarser scale covering most or all of the lesions)
- 4 = Severe/coarse scaling covering almost all or all lesions (coarse, non-tenacious scale predominates)

The composite score falls on a scale of 0 to 4, based on the following:

- Clear 0 = 0 for all three
- Almost clear 1 = mean > 0 to < 1.5
- Mild 2 = mean ≥ 1.5 to < 2.5
- Moderate 3 = mean ≥ 2.5 to < 3.5
- Severe 4 = mean ≥ 3.5

The PGA is more subjective than the PASI in that there is no attempt to quantify the individual elements of plaque morphology or BSA involvement.[44,47] There have also been fewer studies using PGA than PASI. This outcome is considered reliable using test–retest data (1% to 3% variability[47] and intraclass correlation coefficient [ICC] = 0.852) and internal consistency (Cronbach's alpha > 0.8 consistently from week 2 measurements onward).[48] However, inter-rater reliability due to variability, especially in untrained observers, is poor.[47] Many studies now employ only the final value of clear or almost clear as treatment success. Although it would seem the PGA is less likely to be open to interpretation, different studies have used different definitions of clear or almost clear, making comparisons between treatments difficult.[42,47] Construct and content validity are considered strong within a study, but comparison with other studies, as well as relationships to other methods, are problematic due to the variability in data collection, analysis, and reporting method.[47] An MCID in patients with plaque psoriasis was not identified.

Psoriasis Symptoms Scale

The PSS is a patient-reported outcome to assess the severity of psoriasis symptoms. Pain, redness, itching, and burning are rated by patients on a five-point Likert scale, from 0 (none) to four (very severe). In UltIMMA-1 and UltIMMA-2, the PSS was self-administered by patients using a daily diary from visits 2 to 6 and completed during clinics from visit 7 onward. Patients were asked to rate the severity of their symptoms over the past 24 hours using the following questions:

- How severe was your pain from your psoriasis during the past 24 hours?
- How severe was the redness from your psoriasis during the past 24 hours?
- How severe was your itching from your psoriasis during the past 24 hours?
- How severe was your burning from your psoriasis during the past 24 hours?
  - None
  - Mild
  - Moderate
  - Severe
  - Very severe

The PSS is based on two similar instruments, the Psoriasis Symptom Inventory (PSI) and the Psoriasis Symptom Diary (PSD), which have evidence of validity and reliability. The PSI includes eight items that assess itching, redness, scaling, burning, stinging, cracking,

flaking, and pain, and are measured using five-point Likert-type scales ranging from 0 (not at all severe) to 4 (very severe).[53-55] Convergent and discriminant validity were used to evaluate the construct validity of the PSI based on at least a moderate correlation and small correlation, respectively, to the DLQI (item and domain scores) and SF-36 version 2 (subscale and component summary scores).[53,55,65] Using this method, the PSI was shown to have construct validity.[53,55,65] The PSI is also considered reliable as per excellent test–retest (reported as greater than 0.70 in three studies) and internal consistency data (reported as greater than 0.90 in two studies)[53,55,65] and responsiveness based on the known-groups approach, as it was able to detect a statistically significant difference when the mean PSI score had changed, compared with PASI and sPGA scores[55,65] and the patient global assessment.[53] One of the limitations of the PSI is that the majority of the study populations included in the studies validating the instrument were white, potentially limiting the generalizability of the results. The PSD was developed by interviewing 29 patients (majority white) with plaque psoriasis and identifying key plaque psoriasis–related symptoms and impacts.[57] The instrument consists of 20 items and patients rate each item based on 24-hour recall on a scale of 0 to 10.[57] The PSD has been shown to have adequate reliability (ICC > 0.80, aside from item of skin colour), to be significantly related to criterion measures (PASI and investigator's global assessment), and to have generated change scores that were synchronous with changes in PASI, global assessment, and DLQI.[56]

Appendix 6: Summary of Other Studies

Objective

The primary objective of the open-label extension (OLE) trial (M15997, 1311.31) was to evaluate the long-term safety and tolerability of risankizumab for plaque psoriasis. The secondary objective was to evaluate long-term efficacy.

Trial Description

M15997 is a phase III, single-arm, open-label, multi-centre study that is ongoing. To be eligible, patients must have completed one of the lead-in phase II or III studies (i.e., IMMhance, UltIMMA-1, UltIMMA-2, IMMvent, study 1311.38, and study M16-178) and require prolonged risankizumab therapy for moderate to severe plaque psoriasis. Two thousand patients from the lead-in studies are planned for enrolment. As of the data cut-off of the interim analysis ([redacted]), [redacted] patients had entered the extension study from [redacted] sites and across [redacted] countries. [redacted]

[redacted]

The Clinical Study Report for M15997 presented interim results and focused on a subset of eligible patients who received ustekinumab or adalimumab in a lead-in study and switched to risankizumab at entry into the OLE study.

Results

Patient Disposition

Table 28 shows the patient populations included in the interim analysis. At data cut-off, [redacted] patients were previously treated with ustekinumab from the UltIMMA-1 and UltIMMA-2 lead-in studies and were switched to risankizumab at entry into the OLE study. There were no discontinuations among patients who switched from ustekinumab to risankizumab.

From the IMMvent lead-in study, a total of [redacted] patients who were randomized to adalimumab switched to risankizumab in the OLE study. There were [redacted] in this subset due to [redacted]. In Part B of IMMvent (16 weeks), patients originally randomized to adalimumab were either switched to risankizumab if they were nonresponders (achieved less than Psoriasis Area and Severity Index [PASI] 50), re-randomized to risankizumab or adalimumab (if PASI 50 to < PASI 90), or continued on adalimumab if they were responders (achieved PASI 90). The interim analyses for the OLE study focused on patients who were re-randomized to adalimumab at entry of Part B (N = [redacted]) and adalimumab responders who continued on treatment at entry of Part B (N = [redacted]). The total of [redacted], therefore, represents all patients in IMMvent who switched from adalimumab to risankizumab at entry to the OLE study.

Table 28: Patient Populations Analyzed in the Open-Label Extension Study

Population	Definition	N (%)	Outcomes
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
	[redacted]	[redacted]	
	[redacted]	[redacted]	
	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Efficacy

Health-related quality of life (HRQoL) data were available for only a small number of patients at week 24. The data for the Dermatology Life Quality Index (DLQI) are presented in Table 29. Table 30 and Table 31 provide data for the primary PASI outcomes (PASI 75, 90, and 100) and static Physician Global Assessment (sPGA) scores, respectively, at entry into the OLE study and at week 12.

Table 29: Selected Health-Related Quality of Life Outcomes in the Open-Label Extension Study

	N		DLQI 0 n (%)		DLQI 0 or 1 n (%)	
	OLE Entry	Week 24	OLE Entry	Week 24	OLE Entry	Week 24
[redacted]						
[redacted]						
[redacted]						

ADA = adalimumab; DLQI = Dermatology Life Quality Index; OLE = open-label extension; RZB = risankizumab; SE = standard error; UST = ustekinumab.

Table 30: Primary Psoriasis Area and Severity Index Outcomes in the Open-Label Extension Study

	N		PASI 75 n (%)		PASI 90 n (%)		PASI 100 n (%)	
	OLE Entry	Week 12	OLE Entry	Week 12	OLE Entry	Week 12	OLE Entry	Week 12
[redacted]								
[redacted]								
[redacted]								

ADA = adalimumab; OLE = open-label extension; PASI = Psoriasis Area and Severity Index; RZB = risankizumab; UST = ustekinumab.

Table 31: Static Physician Global Assessment in the Open-Label Extension Study

	N		sPGA Clear / Almost Clear n (%)		sPGA Clear n (%)	
	OLE Entry	Week 12	OLE Entry	Week 12	OLE Entry	Week 12
[redacted]						
[redacted]						
[redacted]						

ADA = adalimumab; OLE = open-label extension; RZB = risankizumab; sPGA = static Physician Global Assessment; UST = ustekinumab.

Safety

Table 32 indicates the treatment-emergent adverse events (TEAEs) documented in patients who received risankizumab in the OLE up to data cut-off; who switched from ustekinumab to risankizumab; and who switched from adalimumab to risankizumab at entry of the OLE study. A TEAE was defined as any event with an onset after the first dose of risankizumab (either the lead-in study or OLE) and within 105 days after the last dose of the study drug.

Table 32: Treatment-Emergent Adverse Events in the Open-Label Extension Study

	ALL_RZB (N = 1,392) n (%)	UST_RZB (N = 169) n (%)	ADA_RZB (Re-Randomized to ADA) (N = 49) n (%)	ADA_RZB (Responders) (N = 130) n (%)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Severe AE (grade 3 or 4)	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
MACE	[redacted]	[redacted]	[redacted]	[redacted]
Serious infection	[redacted]	[redacted]	[redacted]	[redacted]
Tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]
Malignancy	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity[a]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic events ALT increase AST increase GGT increase	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MACE = major adverse cardiovascular event; RZB = risankizumab; SAE = serious adverse event; UST = ustekinumab.

[a] No cases of anaphylactic reaction.

Among patients who switched from ustekinumab to risankizumab (N = [redacted]), AEs (defined according to version 20 of the Medical Dictionary for Regulatory Activities) that occurred in two or more patients, included [redacted]. Among patients who switched from adalimumab to risankizumab at entry to the OLE study (N = [redacted]), adverse events (AEs) that occurred in two or more patients included [redacted].

Conclusion

The interim results from the OLE study suggest that efficacy was maintained with risankizumab after switching from ustekinumab or adalimumab. These results, however, are preliminary and are based on a subset of the full planned cohort of 2,000 patients. The limitations of the study, which include its open-label design and absence of any comparator group, must also be considered when interpreting the relevance of the results. Without a control group, it is difficult to determine if efficacy is maintained or if the AE profile changes after switching to risankizumab. Also, no washout periods were established between the switch from ustekinumab or adalimumab to risankizumab, which may have led to lingering effects of the previous treatments. A [redacted] experienced an AE. At the time of data cut-off, most patients received [redacted] of risankizumab during the OLE and a [redacted] percentage of patients were not available for follow-up at the 12-week assessment for PASI and sPGA (about [redacted] of patients were evaluated at 12 weeks), or at the 24-week assessment for HRQoL ([redacted] patients who switched from ustekinumab and [redacted] patients who switched from adalimumab) at the time of data cut-off. More long-term data are still required to understand the prolonged efficacy (i.e., skin clearance and quality of life) and safety of risankizumab for moderate to severe plaque psoriasis.

Appendix 7: Summary of Indirect Comparisons

Introduction and Background

There is an absence of head-to-head studies comparing risankizumab against the other biologics — other than ustekinumab and adalimumab — that are used to treat moderate to severe plaque psoriasis in adult patients. The objective of this appendix is to summarize and critically appraise the evidence available regarding the comparative efficacy and safety of risankizumab versus other treatments through indirect treatment comparison (ITC).

Methods

The manufacturer submitted one ITC that was reviewed, summarized, and critically appraised.[66] The CADTH Common Drug Review (CDR) conducted an independent literature search for published ITCs that compared risankizumab with other relevant comparators for the treatment of moderate to severe plaque psoriasis in adult patients; one additional publication was identified.[67]

Description of Indirect Treatment Comparisons Identified

Table 33 presents the population, interventions, comparisons, outcomes, and study design (PICOS) criteria for each ITC identified.

Table 33: Populations, Interventions, Comparisons, Outcomes, and Study Design Criteria for Study Inclusion

	Manufacturer-Sponsored and -Submitted ITC 2018[66]	ICER 2018[67]
Population	[redacted]	Adult patients with moderate to severe plaque psoriasis
Intervention	[redacted]	Immunomodulating drugs used for the treatment of plaque psoriasis
Comparators	[redacted]	Placebo Any of the interventions of interest
Outcomes	[redacted]	***Outcomes assessed in the NMA*** PASI 50 PASI 75 PASI 90
Study design	[redacted]	***Studies included in the NMA*** Phase III randomized controlled trials
Other	[redacted]	Published in English

CDR = CADTH Common Drug Review; ICER = Institute for Clinical and Economic Review; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index.

Source: Manufacturer's CDR submission for risankizumab[39] and Institute for Clinical and Economic Review, *Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value* (2018).[67]

Review and Appraisal of Indirect Treatment Comparisons

Review of the Manufacturer-Sponsored Indirect Treatment Comparison

Objectives and Rationale for the Manufacturer-Sponsored Indirect Treatment Comparison

The objective of the manufacturer-sponsored ITC was to conduct a network meta-analysis (NMA) of efficacy outcomes (i.e., Psoriasis Area and Severity Index [PASI] 50, PASI 75, PASI 90, and PASI 100) for existing and pipeline treatments (including risankizumab) among patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Methods for the Manufacturer-Sponsored Indirect Treatment Comparison

Study Eligibility and Selection Process

[redacted]

[redacted]

[redacted]

Data Extraction

The publication date, patient information, intervention information, and outcomes were extracted. Select study and patient characteristics are presented in Table 34.

[redacted]

[redacted]

Table 34: Included Studies and Select Patient Characteristics

Study Name (Author Year)	Treatment	Number of Patients (ITT)	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
[redacted]									

Study Name (Author Year)	Treatment	Number of Patients (ITT)	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study Name (Author Year)	Treatment	Number of Patients (ITT)	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Study Name (Author Year)	Treatment	Number of Patients (ITT)	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
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Study Name (Author Year)	Treatment	Number of Patients (ITT)	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
[redacted]									

Study Name (Author Year)	Treatment	Number of Patients (ITT)	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
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Study Name (Author Year)	Treatment	Number of Patients (ITT)	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
[redacted]									

b.i.w. = twice weekly; e.o.w. = every other week; DLQI = Dermatology Life Quality Index; FI = fixed interval; ITT = intention-to-treat; NR = not reported; PASI = Psoriasis Area and Severity Index; q.4.w. = every 4 weeks; q.w. = once weekly; RAN = re-treatment as needed.

Source: Manufacturer's CDR submission for risankizumab.[39]

Comparators

[redacted]

Outcomes

[redacted]

Quality Assessment of Included Studies

[redacted]

[redacted][68][redacted]

Evidence Network

Figure 5: Network of Trials for the Base-Case Analysis of Risankizumab Versus Other Interventions

Figure 5 contained confidential information and was removed at the request of the manufacurer.

Source: Manufacturer's CDR submission for risankizumab.[39]

Indirect Comparison Methods

[redacted]

[redacted]

Results

[redacted]

[redacted]

[redacted]

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[redacted]

Table 35: Results of the Network Meta-Analysis for Achieving a PASI 50 Response: Base Case and Sensitivity Analyses

Treatment	Base-Case Analysis: Adjusted Random-Effects Model		Estimated Response Rate Under Unadjusted Random-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Adjusted Fixed-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Expanded Network Adjusted Random-Effects Model (Median %, 95% CrI)
	Risankizumab 150 mg Versus: (Median Relative Risk [95% CrI])	Estimated Response Rate (Median %, 95% CrI)			
[redacted]					

Treatment	Base-Case Analysis: Adjusted Random-Effects Model		Estimated Response Rate Under Unadjusted Random-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Adjusted Fixed-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Expanded Network Adjusted Random-Effects Model (Median %, 95% CrI)
	Risankizumab 150 mg Versus: (Median Relative Risk [95% CrI])	Estimated Response Rate (Median %, 95% CrI)			
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b.i.w. = twice a week; CrI = credible interval; e.o.w. = every other week; NR = not reported; PASI = Psoriasis Area and Severity Index; q.2.w. = once every 2 weeks; q.4.w. = once every 4 weeks; q.8.w. = once every 8 weeks; q.12.w. = once every 12 weeks; q.w. = once weekly.

Note: Bolded and italicized results indicate relative risks with 95% CrI that exclude the null.

Source: Manufacturer's CDR submission for risankizumab.[39]

Table 36: Results of the Network Meta-Analysis for Achieving a PASI 75 Response: Base Case and Sensitivity Analyses

Treatment	Base-Case Analysis: Adjusted Random-Effects Model		Estimated Response Rate Under Unadjusted Random-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Adjusted Fixed-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Expanded Network Adjusted Random-Effects Model (Median %, 95% CrI)
	Risankizumab 150 mg Versus: (Median Relative Risk [95% CrI])	Estimated Response Rate (Median %, 95% CrI)			
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Treatment	Base-Case Analysis: Adjusted Random-Effects Model		Estimated Response Rate Under Unadjusted Random-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Adjusted Fixed-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Expanded Network Adjusted Random-Effects Model (Median %, 95% CrI)
	Risankizumab 150 mg Versus: (Median Relative Risk [95% CrI])	Estimated Response Rate (Median %, 95% CrI)			
[redacted]					

b.i.w. = twice a week; CrI = credible interval; e.o.w. = every other week; NR = not reported; PASI = Psoriasis Area and Severity Index; PASI 50, 75, 90, 100 = a 50%, 75%, 90%, or 100% decrease from baseline PASI; q.2.w. = once every 2 weeks; q.4.w. = once every 4 weeks; q.8.w. = once every 8 weeks; q.12.w. = once every 12 weeks; q.w. = once weekly.

Note: Bolded and italicized results indicate relative risks with 95% CrI that exclude the null.

Source: Manufacturer's CDR submission for risankizumab.[39]

Table 37: Results of the Network Meta-Analysis for Achieving a PASI 90 Response: Base Case and Sensitivity Analyses

Treatment	Base-Case Analysis: Adjusted Random-Effects Model		Estimated Response Rate Under Unadjusted Random-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Adjusted Fixed-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Expanded Network Adjusted Random-Effects Model (Median %, 95% CrI)
	Risankizumab 150 mg Versus: (Median Relative Risk [95% CrI])	Estimated Response Rate (Median %, 95% CrI)			
[redacted]					

Treatment	Base-Case Analysis: Adjusted Random-Effects Model		Estimated Response Rate Under Unadjusted Random-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Adjusted Fixed-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Expanded Network Adjusted Random-Effects Model (Median %, 95% CrI)
	Risankizumab 150 mg Versus: (Median Relative Risk [95% CrI])	Estimated Response Rate (Median %, 95% CrI)			
[redacted]					
[redacted]					
[redacted]					

b.i.w. = twice a week; CrI = credible interval; e.o.w. = every other week; NR = not reported; PASI = Psoriasis Area and Severity Index; PASI 50, 75, 90, 100 = a 50%, 75%, 90%, or 100% decrease from baseline Psoriasis Area and Severity Index; q.2.w. = once every 2 weeks; q.4.w. = once every 4 weeks; q.8.w. = once every 8 weeks; q.12.w. = once every 12 weeks; q.w. = once weekly.

Note: Bolded and italicized results indicate relative risks with 95% CrI that excludes the null.

Source: Manufacturer's CDR submission for risankizumab.[39]

Table 38: Results of the Network Meta-Analysis for Achieving a PASI 100 Response: Base Case and Sensitivity Analyses

Treatment	Base-Case Analysis: Adjusted Random-Effects Model		Estimated Response Rate Under Unadjusted Random-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Adjusted Fixed-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Expanded Network Adjusted Random-Effects Model (Median %, 95% CrI)
	Risankizumab 150 mg Versus: (Median Relative Risk [95% CrI])	Estimated Response Rate (Median %, 95% CrI)			
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Treatment	Base-Case Analysis: Adjusted Random-Effects Model		Estimated Response Rate Under Unadjusted Random-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Adjusted Fixed-Effects Model (Median %, 95% CrI)	Estimated Response Rate Under Expanded Network Adjusted Random-Effects Model (Median %, 95% CrI)
	Risankizumab 150 mg Versus: (Median Relative Risk [95% CrI])	Estimated Response Rate (Median %, 95% CrI)			
[redacted]					

b.i.w. = twice a week; CrI = credible interval; e.o.w. = every other week; NR = not reported; PASI = Psoriasis Area and Severity Index; q.2.w. = once every 2 weeks; q.4.w. = once every 4 weeks; q.8.w. = once every 8 weeks; q.12.w. = once every 12 weeks; q.w. = once weekly.

Note: Bolded and italicized results indicate relative risks with 95% CrI that excludes the null.

Source: Manufacturer's CDR submission for risankizumab.[39]

Table 39: Safety Outcomes

Treatment	Estimated Odds Ratio of any Adverse Event (OR, 95% CrI)	Estimated Odds Ratio of Serious Adverse Events (OR, 95% CrI)	Estimated Odds Ratio of Discontinuation Due to Adverse Events (OR, 95% CrI)
Risankizumab Versus			
[redacted]			

b.i.w. = twice a week; CrI = credible interval; mg = milligram; NR = not reported; OR = odds ratio; q.2.w. = once every 2 weeks; q.4.w. = once every 4 weeks; q.8.w. = once every 8 weeks; q.12.w. = once every 12 weeks; q.w. = once weekly.

Note: Bolded and italicized results indicate ORs with 95% CrI that excludes the null.

Source: Manufacturer's CDR submission for risankizumab.[39]

Critical Appraisal

The manufacturer's rationale for conducting the ITC (i.e., absence of head-to-head studies that have compared risankizumab against most other relevant biologics) and the objectives of the ITC (to compare the efficacy of risankizumab with all other approved biologics for the treatment of moderate to severe chronic plaque psoriasis) were clearly reported. According to the clinical expert consulted by CDR for this review, the biologic comparators and the dosages used were appropriate. A comprehensive systematic review was performed with a two-stage dual-selection process whereby articles were first selected based on titles and abstracts and then full-text articles were retrieved and their inclusion criteria ascertained. Risk of bias was assessed using a seven-criteria checklist provided in section 2.5 of the National Institute for Health and Care Excellence (NICE) single technology appraisal user guide, and detailed results of these assessments were provided. Two independent reviewers conducted the screening and data extraction, but it is unclear if this was the case in assessing the quality of the studies. Both the inclusion and exclusion criteria used for screening were provided and lists of both included and excluded references with accompanying reasons were reported. A figure of the network was provided.

While all of the information pertaining to the quality of the individual studies was present, it was evident that, in the majority of studies, there was a lack of reporting regarding at least one of the domains of the study quality checklist. Many studies were lacking sufficient

information to ascertain their true validity. Therefore, this lack of verification regarding the risk of bias in these trials might have affected the results of the NMA and may lead to increased uncertainty surrounding the NMA conclusions. The manufacturer-submitted NMA did not specify a course of action to be taken in case a study was found to be of low quality. Also, there was no sensitivity analysis to address the potential effect of studies that lack sufficient information for validity assessment; as such, the uncertainty in the results caused by the potential of low-quality studies is not quantifiable.

Some of the strengths of the NMAs included the performance of and a comparison of the random-effects and fixed-effects models. In addition, the manufacturer performed an NMA meta-regression model on placebo response to account for variation in the response rate in placebo arms, and conducted a sensitivity analysis comparing the results of the adjusted model with the unadjusted model. Adjusting for the variation in response rates in the placebo groups across trials seems to be NICE's preferred approach, rather than using an unadjusted analysis.[68] There are limitations to the adjusting for placebo response because there is an assumption that study and patient characteristics (which are effect modifiers of the relative treatment effect) are also prognostic factors of the outcome with placebo.[69,70] And, given it is unclear to what extent placebo response is an adequate proxy for specific characteristics or effect modifiers, uncertainty remains as a result of such analysis. While the manufacturer used the placebo response rate in its NMA regression model to attempt to account for potential variability in effect modifiers, it is unclear if these effect modifiers have the same level of effect on the active arms. A sensitivity analysis to better explore the effects of these outliers on the analyses would have been useful in reducing the uncertainty of the analysis.

The manufacturer provided efficacy outcomes based on the PASI response, but did not provide any analysis of the other efficacy outcomes covered in this CDR report. While the NMA has also provided analysis of safety outcomes based on the adverse events, serious adverse events, and discontinuation due to adverse events, these results may have limited generalizability due to the short duration of the included trials and the fact that these trials were not designed to capture differences in safety outcomes. While the induction periods are important in the treatment of patients with moderate to severe chronic plaque psoriasis, NMA analyses on longer treatment durations would be beneficial in order to ascertain the long-term efficacy and tolerability of the various biologics. However, it is acknowledged that many (if not the majority) of the trials for psoriasis drug treatments are not adequately designed to evaluate long-term comparative efficacy and safety, which may have precluded an indirect analysis of such data.

Other limitations included the restriction of the interventions to the NICE-approved dosage and regimens. This might have excluded several Health Canada–approved regimens, including the Health Canada–approved dosage of 50 mg of etanercept twice weekly. In addition, the NMA submitted by the manufacturer did not include certolizumab, which has been recently approved for the treatment of plaque psoriasis in Canada. Also, the literature search was conducted in December 2017; since then, several trials have been published that might have been included in the NMA and might have affected the results. The manufacturer's NMA did not include information regarding the method of determining model convergence or an inconsistency model to assess the assumption of consistency. In addition, there was inconsistent or an absence of reporting of key data in the included studies. Also, the fact that only English-language articles were included has the potential to reduce confidence in the results if any key articles were missed.

Overall, the limitations that increase uncertainty in the data can be summarized as follows:

- Lack of an updated search: Several new trials were published in 2018, which may have affected the outcome of the analysis.
- Restricting the included interventions to the NICE-approved drugs and dosages: This has resulted in the exclusion of several studies that assessed drugs using the Health Canada–approved indication and dose.
- Lack of sensitivity analyses addressing potential studies with outlier values for potential effect modifiers.
- Lack of an inconsistency model to determine if direct and indirect evidence in the network are similar.

Review of the Indirect Treatment Comparison by the Institute for Clinical and Economic Review, 2018

Objectives and Rationale for Indirect Treatment Comparison by the Institute for Clinical and Economic Review

The objective of the systematic review and NMA by the Institute for Clinical and Economic Review (ICER)[67] was to update a previous systematic review and NMA, published in 2016, of immunomodulator treatment for moderate to severe plaque psoriasis in adults.

Methods for Indirect Treatment Comparison by the Institute for Clinical and Economic Review

Study Eligibility and Selection Process

English-language randomized controlled trials (RCTs) were eligible to be included in the ITC if they met the following a priori inclusion criteria: adult patients with moderate to severe plaque psoriasis receiving treatment with immunomodulators.

Outcomes of interest were the proportion of patients achieving PASI 50, 75, 90, and 100 at the end of the induction period for each therapy.

Appropriate systematic review methods were employed in assessing study inclusion eligibility. The literature search was conducted for articles published from January1, 1996 to January 2, 2018 and included multiple databases (Embase, MEDLINE, and Cochrane Library databases) in addition to grey literature. Two reviewers independently screened titles, abstracts, and full-text articles for inclusion, with disagreements resolved by a third reviewer.

Data Extraction

For each study included in the review, study design details, patient information, intervention information and efficacy, and safety outcomes were extracted. A total of 53 RCTs were included in the NMA. In comparison with the manufacturer-submitted NMA, The ICER NMA contained 12 studies that were not present in the manufacturer-submitted NMA. Conversely, the manufacturer-submitted NMA contained 12 studies not present in the ICER NMA. This discrepancy is due to the fact the ICER NMA excluded phase II and pilot RCTs, while the manufacturer-submitted NMA excluded studies with a dose not recommended by NICE.

The mean age was generally consistent across trials (range of means: 39 to 50 years; median: 45) and comparable with respect to duration of psoriasis (range of means: 11 to 22

years; median: 18). Baseline PASI scores across trials ranged from 15 to 33 (median: 20). Details of the baseline characteristics of the included studies can be found in Table B1 of the ICER original report.[67]

Comparators

Comparators and their dosing regimens were appropriate for Canadian decision-makers. All comparators were biologics; therefore, they would be considered appropriate in terms of when they would be used in the treatment algorithm. Doses of the same intervention were pooled together for the analysis.

Outcomes

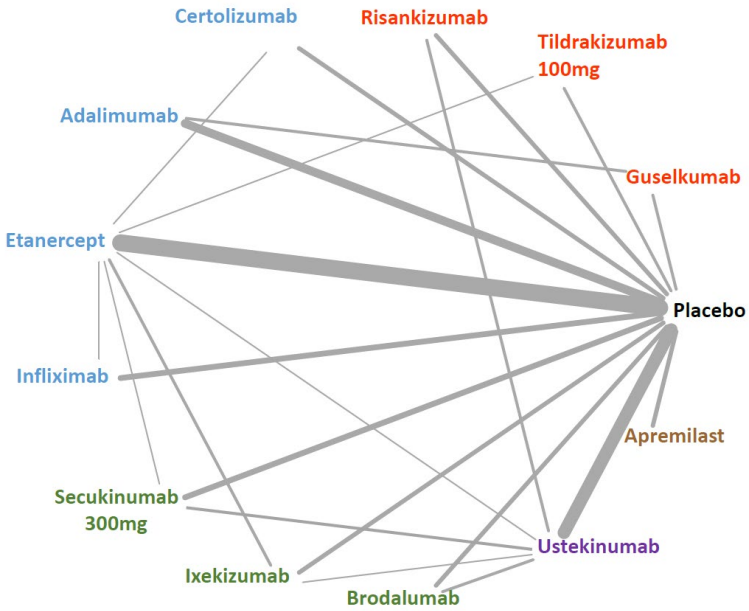
The NMA assessed PASI 50, PASI 75, and PASI 90. Key efficacy outcomes of interest that were identified in the CDR review protocol, such as results of Dermatology Life Quality Index and global assessment, were not analyzed in the NMA; similarly, key safety outcomes (adverse events, serious adverse events and withdrawals due to adverse events) were not analyzed in this NMA.

Quality Assessment

The ICER review utilized the US Preventive Services Task Force criteria to determine the quality of the included studies. It was determined that all included studies were of good or fair quality. No detailed reporting of each study was available in the published report.[67]

Evidence Network

Figure 6: Evidence Network for Base-Case Analysis of Psoriasis Area Severity Index Response



Note: The lines connecting therapies represent direct comparisons observed in a clinical trial; the number of lines and their thickness represent how many trials measured the contrast.

Source: Reproduced (with permission) from *Targeted Immunomodulators for the Treatment of Moderate to Severe Plaque Psoriasis: Effectiveness and Value*, April 27, 2018, produced by the Institute for Clinical and Economic Review.[67]

Meta-Analysis and Indirect Comparison for the Indirect Treatment Comparison by the Institute for Clinical and Economic Review

A placebo-adjusted Bayesian NMA random-effects model was employed for the base-case analysis to calculate the efficacy outcome of PASI response. The model used a multinomial likelihood approach with a probit link to model PASI outcomes as ordered categorical data with four groups: < PASI 50, PASI 50, PASI 75, and PASI 90. Through Markov chain Monte Carlo modelling, the NMA used a non-informative prior, 50,000 burn-in cycles, and an additional 50,000 iterations using three chains; convergence was determined through trace plots. The NMA provided the efficacy output for every possible treatment comparison in terms of relative risk (RR) and 95% credible intervals.

No method to assess potential inconsistency, statistical heterogeneity, or model fit was described in the published report.

Three additional sensitivity analyses were conducted: patients with psoriatic arthritis, patients with previous biologic therapy exposure, and Asian studies.

Results of the Indirect Treatment Comparison by the Institute for Clinical and Economic Review

Psoriasis Area and Severity Index 50, 75, and 90 Responses

The base-case analyses were performed using a random-effects model with adjustment for placebo response. The base-case results of the NMA models are presented in Table 40.

Risankizumab had a significantly better result (with a 95% credible interval) at achieving PASI 50, PASI 75, and PASI 90 responses than placebo, apremilast, etanercept, tildrakizumab, certolizumab, adalimumab, ustekinumab, infliximab, and secukinumab. Risankizumab did not show a significantly favourable result when compared with ixekizumab, brodalumab, or guselkumab.

Three sensitivity analyses were performed by excluding studies that included patients with psoriatic arthritis, patients with previous biologic therapy exposure, and Asian studies. Results of these three sensitivity analyses (not reported here) were similar to base-case analysis results.

Table 40: Base-Case Comparisons From the Network Meta-Analysis of the Median Relative Risk (95% Credible Interval) of PASI 50, 75, and 90 Responses

Treatment	PASI 50 (RR, 95% CrI)	PASI 75 (RR, 95% CrI)	PASI 90 (RR, 95% CrI)
Risankizumab Versus			
Placebo	**6.22 (4.84 to 8.14)**	**16.54 (12 to 23.47)**	**55.87 (37.9 to 83.87)**
Apremilast	**1.61 (1.42 to 1.9)**	**2.44 (1.98 to 3.12)**	**4.36 (3.24 to 6.07)**
Etanercept	**1.32 (1.23 to 1.43)**	**1.74 (1.54 to 1.98)**	**2.62 (2.19 to 3.16)**
Tildrakizumab	**1.18 (1.1 to 1.28)**	**1.42 (1.26 to 1.66)**	**1.91 (1.55 to 2.42)**
Certolizumab	**1.12 (1.07 to 1.2)**	**1.3 (1.18 to 1.47)**	**1.63 (1.39 to 1.99)**

Treatment	PASI 50 (RR, 95% CrI)	PASI 75 (RR, 95% CrI)	PASI 90 (RR, 95% CrI)
Adalimumab	**1.1 (1.07 to 1.16)**	**1.26 (1.17 to 1.38)**	**1.54 (1.36 to 1.8)**
Ustekinumab	**1.11 (1.07 to 1.16)**	**1.26 (1.18 to 1.37)**	**1.56 (1.39 to 1.78)**
Infliximab	**1.05 (1.02 to 1.09)**	**1.12 (1.04 to 1.22)**	**1.25 (1.09 to 1.47)**
Secukinumab	**1.03 (1.01 to 1.06)**	**1.07 (1.02 to 1.14)**	**1.16 (1.04 to 1.3)**
Ixekizumab	1.00 (0.98 to 1.02)	1.00 (0.96 to 1.05)	1.07 (0.96 to 1.19)
Brodalumab	1.01 (0.99 to 1.03)	1.03 (0.98 to 1.09)	1.03 (0.92 to 1.16)
Guselkumab	1.01 (0.99 to 1.03)	1.02 (0.96 to 1.08)	1.01 (0.91 to 1.11)

CrI = credible interval; PASI = Psoriasis Area and Severity Index; RR = relative risk.

Risk ratios in bold indicate significant differences.

Source: Adapted (with permission) from *Targeted Immunomodulators for the Treatment of Moderate to Severe Plaque Psoriasis: Effectiveness and Value*, April 27, 2018, produced by the Institute for Clinical and Economic Review.[67]

Critical Appraisal of Indirect Treatment Comparison by the Institute for Clinical and Economic Review

The rationale for conducting the ITC (i.e., to update the 2016 evidence-based review) and the objectives of the ITC were clearly reported. According to the clinical expert consulted by CDR for this review, the biologic comparators and dosages used were appropriate. A comprehensive systematic review was performed with a two-stage dual-selection process, whereby articles were first selected based on titles and abstracts and then full-text articles were retrieved and their inclusion criteria ascertained. Risk of bias was assessed using the checklist from the US Preventive Services Task Force criteria, although the detailed results of these assessments were not provided and no plan regarding the handling of a potentially high risk of bias in the studies was reported. Two independent reviewers conducted the screening and data extraction. Both the inclusion and exclusion criteria used for screening were provided and lists of both included and excluded references with accompanying reasons were reported. A figure of the network was provided.

Some of the strengths of the NMAs included the use of the random-effects model. In addition, the NMA was adjusted for placebo response, although no comparison with an unadjusted model was provided. Adjusting for the variation in response rates in the placebo groups across trials seems to be NICE's preferred approach, rather than using an unadjusted analysis.[68] There are limitations to the adjusting for placebo approach because there is an assumption that study and patient characteristics (that are effect modifiers of the relative treatment effect) are also prognostic factors of the outcome with placebo.[69,70] And, given it is unclear to what extent placebo response is an adequate proxy for specific characteristics or effect modifiers, uncertainty remains as a result of such analysis. The use of placebo response rate is an attempt to account for potential variability in effect modifiers, but it is unclear if these effect modifiers have the same level of effect on the active arms. A sensitivity analysis to better explore the effects of trials with outliers on the analyses would have been useful in reducing the uncertainty of the analysis, along with a comparison of an unadjusted model.

The manufacturer provided efficacy outcomes based on the PASI response, but did not provide an analysis of the other efficacy outcomes that are covered in this CDR report. The pairwise results were provided for PASI 50, 75, and 90, but not PASI 100. No analysis of safety outcomes was conducted.

Other limitations included the exclusion of phase II and pilot RCTs, which excluded several studies. The report did not include information regarding assessment of model fitness or an inconsistency model to assess the assumption of consistency.

Overall, the limitations that increase overall uncertainty in the data can be summarized as follows:

- Exclusion of phase II and pilot RCTs: Several trials were excluded, which may have affected the outcome of the analysis.
- Lack of reporting on model fitness, conducting multiple models to determine best fit, and lack of inconsistency assessment: Assessment of the statistical fitness of various approaches to the data may provide better insight into potential statistical heterogeneity and allow for the potential to provide better fit results, while the lack of an inconsistency model increases uncertainty in the results, as the assumption of consistency has not been tested.
- Lack of sensitivity analyses addressing potential studies with outlier values for potential effect modifiers, as well as for the potential effect of pooling different doses of the same drug.

Conclusion

Two ITCs (one submitted by the manufacturer, and one conducted and published by the ICER) were summarized and critically appraised in this review. Results of the adjusted NMA in both ITCs suggest that over short-term induction-treatment periods (ranging from 10 to 16 weeks), the relative risk of achieving PASI 75 and PASI 90 responses is significantly greater for risankizumab than for placebo, apremilast, etanercept, adalimumab, ustekinumab, infliximab, and secukinumab in patients with moderate to severe chronic plaque psoriasis. Both studies also showed no significant differences for risankizumab versus ixekizumab, brodalumab, or guselkumab. These results were also similar for the efficacy outcome of PASI 100 in the manufacturer-submitted ITC. Safety outcomes were reported in the manufacturer-submitted ITC but not in the ICER ITC; results suggested no significant difference between risankizumab and other interventions in terms of serious adverse events. The relative efficacy and safety of risankizumab in comparison with other biologics beyond the short-term induction periods remains unknown, and health-related quality of life (HRQoL) data were not evaluated in the ITCs; therefore, the safety and HRQoL data of risankizumab compared with other treatments for moderate to severe chronic plaque psoriasis have yet to be fully evaluated. These results seem to support risankizumab as another treatment option that appears to be at least as efficacious as other newer biologics.

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