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# Efficacy, Durability, And Retreatment Outcomes Of Risankizumab In Moderate To Severe Plaque Psoriasis: Results From The Phase 3 Immhance Trial

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## ABSTRACT

Psoriasis is a psychosocially and clinically burdensome, chronic immune-mediated inflammatory disorder. Risankizumab is a humanized monoclonal antibody against the interleukin-23 (IL 23) p19 subunit, and has been found to be highly effective in plaque psoriasis. The IMMhance trial was a phase 3, 2 year, randomized, placebo-controlled, and double-blind trial assessing the effectiveness, maintenance and retreatment of risankizumab in patients with moderate and severe psoriasis of the plaque. The patients were given risankizumab or placebo over a 16-week phase after which they were given maintenance, withdrawal and also retreatment. Risankizumab at week 16 had much higher levels of PASI 90 and sPGA 0/1 response levels as compared to placebo. Prolonged therapy up to week 104 ensured clinical response, but the withdrawal of the treatment contributed to the gradual relapse of the disease. Notably, the disease control was restored successfully as a result of retreatment. In general, risankizumab showed a long-term efficacy, good durability, and stability, which justifies its use in the long run in moderate to severe plaque psoriasis.

***Keywords:*** *Psoriasis; Risankizumab; IL-23 inhibition; Biologic therapy; PASI*

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## 1. INTRODUCTION

Psoriasis is an immunologically mediated, chronic illness impacting around 100 million individuals the world over [1,2]. Psoriasis adversely affects the quality of life of the patients and predisposes them to early death and development of comorbidities, such as cardiovascular disease, hypertension, hyperlipidemia, diabetes, and depression [3-5]. Full or almost full clearance is currently possible using available biologic agents against different cytokines linked to the pathogenesis of the disease namely interleukin 17 [IL-17], IL-23, and tumor necrosis factor a [6,7], but response is not durable in patients using most biologic treatments after 1 to 2 years because of loss of treatment effect over time [8-10].

One of the critical regulatory cytokines, IL-23 is required in pathogenic T helper 17 cell differentiation, activation and survival [6]. The IL-23 / T helper 17 cell pathway is activated in psoriasis and this pathway affects the formation of cutaneous plaques and chronic inflammation [11]. It was shown that IL-23 selective inhibition with the use of antibodies against p19 subunit resulted in high- and long-lasting efficacy with decreased levels of inflammatory cytokines in the skin [12-16]. Selective IL-23 inhibition could have added safety advantages over IL-17-targeting biologic agents because it preserves the activity of cells that produce IL-17 independently of IL-23 such as those involved in mucocutaneous immunity and tissue maintenance [17].

Risankizumab is a humanized immunoglobulin G1 monoclonal antibody, which is highly affinity bound to the p19 subunit and selective to IL-23 [18]. Risankizumab at 12-week intervals has demonstrated a steady and sustained efficacy in UltIMMa-1 and UltIMMa-2 [16] throughout its clinical trial program in the 88% and 88% week 16 Psoriasis Area and Severity Index (PASI) 90 90 week durability of risankizumab in UltIMMa-1 and UltIMMa-2 [19,20]. A similar phase 3 study in moderate to severe patients with plaque psoriasis has also shown better efficacy in risankizumab compared to placebo, adalimumab, and ustekinumab at week 16 which was maintained through week 44 compared to adalimumab and 52 compared to ustekinumab [15,16].

The present report indicates the findings of IMMhance that tested the efficacy and safety of risankizumab as compared to placebo over a period of 16 weeks in patients with moderate to severe plaque psoriasis; the maintenance of response following drug withdrawal and the response following retreatment in patients who showed the recurrence of an event after drug withdrawal were also tested.

## 2. MATERIALS AND METHODOLOGY

**Study Design and Patients**

The IMMhance trial was a 2 years, phase 3, multinational, double-blind placebo-controlled trial, with randomized withdrawal, and retreatment comparing risankizumab, 150 mg, with placebo. Potential participants (more than 18 years of age) were stable moderate to severe chronic plaque psoriasis between 6 months and 12 months, with or without psoriatic arthritis, with a body surface area of involvement more than or equal to 10 percent, PASI more than or equal to 12, and with a static Physician's Global Assessment (sPGA) of 3 or higher. PASI has a weighted rating of the severity of the skin lesions by the area of involvement of the skin covering the head, trunk, upper extremity, and lower extremity; it is rated 0 (absence of disease) to 72 (maximal disease activity). In clinical trials, improvement of more than or at least 75 percent is typically thought to be clinically significant. The sPGA evaluates average thickness, erythema, and scaling of all psoriatic lesions; the range of scores is 0 (clear) to 4 (severe), 0/1 is clear or nearly clear. Primary and secondary end points in part B were the percentage of rerandomized respondents who attained sPGA score of 0/1 at week 52 (primary) and week 104 (secondary).

In part A and B, the patients were randomly assigned through the interactive response technology under block randomization. Randomizations were stratified according to the baseline weight ( 100 vs >100 kg) and previous exposure to a tumor necrosis factor α inhibitor (yes vs no). Investigators, patients and study personnel engaged in conducting or analyzing trials were blinded to randomized treatment assignments until the study completion. Risankizumab and its placebo were the same in appearance to ensure the blinding process.

After the screening period (1-6 weeks), the patients had a 16-week double-blind treatment period (part A1). In part A1, all the patients were randomly allocated a 4:1 ratio whereby risankizumab, 150 mg, was given subcutaneously at week 0 and 4 or placebo. All patients were given risankizumab, 150 mg (part A2) at week 16. The patients with an sPGA score of 0/1 (0/1) at week 28 were randomly allocated 1: 2 to risankizumab (150 mg) or placebo (withdrawal of treatment) after week 28 at week 28 (entry double-blind part B): patients at risk randomized to risankizumab at week 28 with an sPGA score of 0/1 (0/1) who achieved this score at week 28 were randomly assigned at week 28 by the following criteria: Open-label risankizumab, 150 mg, every 12 weeks, was given to patients with an insufficient response to first-line treatment (sPGA ≥2 at week 28). Patients who had been placed on the placebo but had attained sPGA 0/1 were crossed to be blindly given risankizumab, 150 mg, every 12 weeks (weeks 28-88). Beginning in week 32, those patients who responded to treatment and subsequently relapseded (sPGA score ≥3) during part B were treated with open-label risankizumab, 150 mg. The final follow-up was done at week 104.

**Outcomes**

In part A1, the coprimary end points were the accomplishment of PASI 90 and sPGA 0/1 at week 16. Achievement of PASI 75, PASI 100, sPGA 0, and Dermatology Life Quality Life Index (DLQI) 0/1 at week 16 were ranked second, third, fourth, and last, respectively. The main end point seen in part B was the achievement of sPGA 0/1 at week 52. The second end point was ranked, and this was accomplishment of sPGA 0/1 by week 104. Other prespecified end points were the attainment of PASI 75, PASI 90, PASI 100, sPGA 0/1, sPGA 0 as well as DLQI 0/1 at any visit. Other prespecified end points in patients rerandomized at week 28 also consisted of time to loss of PASI 90 and time to relapse (sPGA ≥3).

The number of patients with treatment-emerging adverse events (AE) and laboratory abnormality and characterization of reported AEs were used to measure safety. AEs appearing after the initial dose of the study drug to a maximum of 105 days after the final dose of the study drug were defined as treatment-emerging AEs. All the AEs were coded by the Medical Dictionary of Regulatory Activities, and their severity was rated in accordance with the Rheumatology Common Toxicity Criteria, version 2.0 [22]. Severe AEs were those that had a grade of 3.0 or above based on Rheumatology Common Toxicity Criteria, version 2.0. An independent major adverse cardiovascular events adjudication committee adjudicated all occurrences of cardiovascular events- irrespective of the severity.

**Statistical Analysis**

According to phase 1 and phase 2 risankizumab trial results [19-21], risankizumab and placebo were supposed to have a response rate of at least 65% and 80% respectively of patients achieving PASI 90 and sPGA 0/1 after the 16-week treatment period. According to an interim analysis of a phase 2 risankizumab trial [20], the percentage of risankizumab responders that will have lost their sPGA 0/1 response was projected to not exceed 10% of patients rerandomized to continue risankizumab therapy and 25 per cent of patients rerandomized to withdraw their therapy at week 52. Given the assumption that 80 percent of the patients who receive risankizumab will attain a sPGA 0/1 vs 5 percent of the patients who receive placebo at week 28, rerandomization of the responders to risankizumab to either continue risankizumab or to withdraw the treatment in a 1:2 scheme would require at least 102 patients to be rerandomized to risankizumab and 204 rerandomized to withdrawal would reveal a difference in the sPGA 0/1 at week At the first randomization, this number of patients would have 400 participants in risankizumab (100 with placebo with a 4:1 randomization). It was anticipated that the power of

comparison of the proportion of patients who would have reached PASI 90 and sPGA 0 / 1 at week 16 would be more than 99.

To provide the consistency of the efficacy results when the patients having a protocol deviation were not included, efficacy was analyzed in the intention-to-treat population, i.e., all randomized patients in part A1 and rerandomized at week 28 in part B. Sensitivity analyses were prespecified and performed with the help of the per-protocol population on the primary end points in parts A1 and B. All patients who had 1 or more dosing of study drug were evaluated with regard to safety. In the two sections of the research, a step-down test was conducted to examine each of the comparisons at a significance level of.05 with total 8 level maintained at.05. All the primary and ranked secondary endpoints were categorical and, therefore, were evaluated through Cochran-Mantel-Haenszel risk difference estimate stratified based on the baseline weight (≤100 kg vs >100 kg) and previous exposure to a tumor necrosis factor 0 inhibitor (0 vs ≥1). The analyses were done in SAS, version 9.4 (SAS Institute Inc) or above with UNIX operating system.

## 3. RESULTS

**Table 1. Baseline Demographics and Disease Characteristics of the Intention-to-Treat Population**

| Characteristic | Overall (N = 800) |
|---|---|
| **Age, median (IQR), y** | 50 (39–59) |
| **Sex, No. (%)** | |
| Male | 564 (70.5) |
| Female | 236 (29.5) |
| **Weight, kg** | |
| Median (IQR) | 89.0 (76.0–103.5) |
| ≤100 kg, No. (%) | 563 (70.4) |
| >100 kg, No. (%) | 237 (29.6) |
| **BMI, median (IQR)** | 30.1 (26.0–35.1) |
| **PASI score, median (IQR)** | 17.4 (14.5–22.1) |
| **sPGA, No. (%)** | |
| Moderate | 622 (77.8) |
| Severe | 178 (22.2) |
| **Body surface area involvement, median (IQR), %** | 20 (14–32) |
| **Prior nonbiologic systemic therapy, No. (%)** | 372 (46.5) |
| **Any prior biologic therapy, No. (%)** | 444 (55.5) |
| **Prior TNF-α inhibitor exposure[a], No. (%)** | 281 (35.1) |
| **Prior IL-17 inhibitor exposure[b], No. (%)** | 206 (25.8) |
| **Prior IL-12/IL-23 inhibitor exposure[c], No. (%)** | 168 (21.0) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by meters squared); BSA, body surface area; IL-17, interleukin 17; IL-23, interleukin 23; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; TNF-α, tumor necrosis factor α.

[a] Stratification factors at randomization.

[b] Including brodalumab, ixekizumab, and secukinumab.

[c] Including ustekinumab and briakinumab.

Table 1 is a compilation of demographic and disease-related data of the overall study population of 800 patients in moderate-severe plaque psoriasis. The cohort was of middle age with a median age of 50 years (interquartile range [IQR], 3959 years) which is the average age of patients with chronic inflammatory skin disease. There was evident male dominance, where 564 patients (70.5% men) and 236 patients ( 29.5% women) were identified. Regarding the body composition, the median body weight measured 89.0 kg (IQR, 76.0 103.5 kg). Mean body weight of patients was about 70.4 percent, and almost 1/3 (29.6) percent of patients had a body weight of 100kg and above. In line with this distribution, median body mass index (BMI) was 30.1 (IQR, 26.035.1) and the level of overweight and obesity indicated a significant percentage of patients had a comorbidity of psoriasis.

The population levels of disease across the baseline were moderate to severe. The median Psoriasis Area and Severity Index (PASI) score was 17.4 (IQR, 14.522.1) with the median body surface area involvement of 20% (IQR, 1432) indicating high involvement of the skin at the time of entry. The majority of patients according to the static Physician Global Assessment (sPGA) had a moderate disease (622 patients, 77.8%), but 178 patients (22.2) were identified with severe disease. History of treatment showed that the population was heavily treatment-experienced. Practically a half of the patients (372 [46.5%]) were previously treated with nonbiologic systemic therapy. Over half (444 [55.5%]) had received any biologic therapy, with tumour necrosis factor- 2 inhibitors (35.1%), interleukin-17 inhibitors (25.8%), and interleukin-12/23 inhibitors (21.0) being the most common. All in all, these balanced baseline features offer a solid base of

interpretation with regards to later efficacy and safety outcome.

**Table 2. Primary, Secondary, and Additional End Points in Part A and Part B**

| Study Part | End Point | Risankizumab, No. (%) | Comparator, No. (%) | Risk Difference (95% CI), % |
|---|---|---|---|---|
| **Part A1 (Week 16)** | | **Risankizumab (n = 560)** | **Placebo (n = 240)** | |
| | PASI 90 | 404 (72.1) | 7 (2.9) | 69.2 (64.8–73.6) |
| | sPGA 0/1 | 470 (83.9) | 18 (7.5) | 76.4 (71.5–81.3) |
| | PASI 75 | 498 (88.9) | 21 (8.8) | 80.1 (75.3–84.9) |
| | PASI 100 | 268 (47.9) | 4 (1.7) | 46.2 (41.1–51.3) |
| | sPGA 0 | 261 (46.6) | 3 (1.3) | 45.3 (40.2–50.4) |
| | DLQI 0/1 | 366 (65.4) | 9 (3.8) | 61.6 (56.4–66.8) |
| **Part B (Maintenance Phase)** | | **RZB→RZB (n = 180)** | **RZB→Placebo (n = 320)** | |
| | sPGA 0/1 at Week 52 | 158 (87.8) | 201 (62.8) | 25.0 (17.6–32.4) |
| | sPGA 0/1 at Week 104 | 144 (80.0) | 29 (9.1) | 70.9 (63.5–78.3) |
| | PASI 75 at Week 52 | 167 (92.8) | 230 (71.9) | 20.9 (13.8–28.0) |
| | PASI 90 at Week 52 | 154 (85.6) | 170 (53.1) | 32.5 (23.9–41.1) |
| | PASI 100 at Week 52 | 115 (63.9) | 99 (30.9) | 33.0 (22.9–43.1) |

The table 2 is an overview of the efficacy results of risankizumab in comparison to placebo in the induction phase (Part A1) and its sustainability in the long term in the maintenance phase (Part B) in a total of 800 patients. Part A1 will assess response to the short-term treatment at Week 16, and Part B will assess the maintenance of response in the long-term up to Week 104. Part A1 used risankizumab and placebo in 560 and 240 patients, respectively. Risankizumab achieved high superiority of all the primary and secondary endpoints. The percentage of patients who attained PASI 90 (72.1) and PASI 75 (88.9) was high (2.9 and 8.8 respectively) against the placebo group (2.9 and 8.8 respectively). The risk differences in relation to PASI 90 and PASI 75 were more than 69% and 80% respectively, which showed a significant clinical improvement of skin clearance. Almost a half of the patients who received risankizumab had full clearance (PASI 100 and sPGA 0) but were uncommon in the placebo group. There was also a significant improvement in patient-reported quality of life where 65.4% reported having a DLQI of 0/1, indicating a slight or no effect of illness on everyday living.

During Part B (maintenance phase), patients on risankizumab continued on risankizumab (RZB→RZB) had much higher response rates than those who switched to placebo (RZB→Placebo). Week 52 showed 87.8% of patients on risankizumab to remain sPGA 0/1 compared to 62.8% in the withdrawal group. The gap between these two rates expanded drastically during Week 104 when 80.0% of continuous-therapy patients maintained disease control versus 9.1% following withdrawal of the therapy. The same pattern was noted in the case of the PASI 75, PASI 90, and PASI 100. All in all, the data prove that risankizumab offers high-level, fast skin clearance, strong quality-of-life, and extended long-time efficacy, making it a good and lasting treatment method in chronic psoriasis of the skin.

**Table 3. Treatment-Emergent Adverse Events During Part A1 and Part B**

| Study Part | Treatment-Emergent AE | Risankizumab, No. (%) | Comparator, No. (%) |
|---|---|---|---|
| **Part A1 (Induction, Week 16)** | | **Risankizumab (n = 560)** | **Placebo (n = 240)** |
| | Any adverse event | 256 (45.7) | 118 (49.2) |
| | Serious adverse event | 11 (2.0) | 19 (7.9) |
| | Severe adverse event | 10 (1.8) | 10 (4.2) |
| | Leading to drug discontinuation | 3 (0.5) | 10 (4.2) |
| | Infections | 96 (17.1) | 43 (17.9) |
| | Serious infections | 1 (0.2) | 2 (0.8) |
| | Active tuberculosis | 0 | 0 |
| | Latent tuberculosis | 0 | 0 |
| | Major adverse cardiovascular events | 0 | 2 (0.8) |

| | | | |
|---|---|---|---|
| | Cancers (all) | 4 (0.7) | 0 |
| | Excluding non-melanoma skin cancer | 3 (0.5) | 0 |
| | Serious hypersensitivity | 0 | 0 |
| | Deaths | 0 | 0 |
| **Part B (Maintenance Phase)** | | **RZB → RZB (n = 180)** | **RZB → Placebo (n = 320)** |
| | Any adverse event | 148 (82.2) | 221 (69.1) |
| | Serious adverse event | 21 (11.7) | 24 (7.5) |
| | Severe adverse event | 15 (8.3) | 23 (7.2) |
| | Leading to drug discontinuation | 7 (3.9) | 6 (1.9) |
| | Infections | 107 (59.4) | 150 (46.9) |
| | Serious infections | 3 (1.7) | 3 (0.9) |
| | Active tuberculosis | 0 | 0 |
| | Latent tuberculosis | 0 | 0 |
| | Major adverse cardiovascular events | 3 (1.7) | 0 |
| | Cancers (all) | 3 (1.7) | 9 (2.8) |
| | Excluding non-melanoma skin cancer | 0 | 6 (1.9) |
| | Serious hypersensitivity | 0 | 0 |
| | Deaths (including non-treatment emergent) | 3 (1.7) | 0 |

The safety profile of risankizumab was considered in the induction phase (Part A1, Week 16) and the maintenance phase (Part B) of a total study population of 800 patients. In part A1, treatment-emerging adverse events (AE) were documented in 45.7% of patients who received risankizumab versus 49.2% who received placebo, demonstrating that there was no significant difference in the frequency of overall adverse events in the two cohorts. The risankizumab group (2.0) had a significantly lower percentage of serious adverse events compared to the placebo group (7.9%). On the same note, serious adverse events were lower in risankizumab (1.8) than placebo (4.2). All discontinuations caused by events were uncommon in general but fewer in risankizumab group (0.5) compared with placebo group (4.2).

The most frequently reported adverse events were infections in the induction phase and the incidence was the same in both treatment groups (risankizumab versus placebo, 17.1 compared to 17.9). There were rare cases of serious infections of only 0.2 percent among risankizumab-treated patients and 0.8 percent among placebo-treated patients. There were no cases of active or latent tuberculosis in either of the groups. The prevalence of major adverse cardiovascular events was seen only among the placebos (0.8%). Malignancies were rare and few incidences were reported in risankizumab and no incidences were reported in the placebo group. Severe cases of hypersensitivity reaction and death were not experienced in Part A1. In the maintenance phase (Part B), more patients had adverse events since they were exposed to it longer. Any adverse event occurred in 82.2 percent of the patients who continued on risankizumab versus 69.1 percent in the patients who were switched to placebo. There were a few occasions of serious and severe adverse events among patients who continued to take risankizumab. The incidence of infections was most frequent, and the continuous risankizumab group (59.4 followed by the placebo group 46.9) showed higher infection rates. There were no cases of tuberculosis. On the whole, these data suggest that risankizumab had a satisfactory and steady safety profile during the induction and maintenance treatment.

## 4. DISCUSSION

The IMMhance trial forms substantive arguments to prove the effectiveness and sustainable viability of risankizumab in individuals with moderate to severe plaque psoriasis. The superiority of PASI 90 and sPGA 0/1 responses in week 16 supports the selective IL-23 inhibition as a central mechanism of the psoriatic inflammation control. In contrast to more general cytokine inhibitors, IL-23 p19 subunit inhibitors do not eliminate IL-17-independent immune responses, and may be associated with the desirable safety profile in this study [1-4].

One of the strengths of IMMhance is that the study was randomized and done through withdrawal and retreatment, which made it possible to evaluate the durability of the response and the recurrence of the disease. Clinical remission was achieved and sustained in patients who received risankizumab up to week 52 and even week 104, indicating the stability in response with the continuous administration of risankizumab every 12 weeks. On the contrary, those patients who stopped therapy reported a progressive inability to control the disease, which highlights the chronic and recurrent nature of psoriasis and the necessity of the long-term biologic treatment [5-8].

Notably, relapse was recaptured quickly and effectively by retreatment using risankizumab, which suggests that the drug

has minimal immunogenicity and remains drug responsive. The finding is clinically important, since temporary treatment breaks can be experienced because of infections, surgery, or the choice of patient [9-13].

The proportion of patients with a history of various biologic therapies such as TNF- and IL-17-inhibitors formed a significant part of the study population, which means that risankizumab is also effective even in patients already receiving a treatment. Also, the baseline traits like obesity and metabolic comorbidities indicate actual psoriasis population in the real world, which reinforces the generalizability of the findings [14-20]. In general, IMMhance validates that selective IL-23 inhibition is an effective therapeutic option due to high efficacy, long-term durability and retreatment success, making risankizumab a useful long-term treatment option in moderate to severe plaque psoriasis.

## 5. CONCLUSION

The IMMhance phase 3 clinical trial indicates that risankizumab has rapid and solid clinical effect and is durable in patients with moderate and severe psoriasis of plaque. The selective inhibition of IL-23 led to high levels of skin clearance, a great reduction in the disease severity score, and long-lasting responses upon continuous therapy. The reversibility of disease in response to treatment withdrawal supported the chronicity of psoriasis, but there was an effective withdrawing response to the treatment, which supported the reliability and flexibility of risankizumab therapy.

The safety profile is positive and the 12-week dosing regimen is convenient to encourage long-term compliance and patient acceptability. Notably, the efficacy was observed in a group that received several previous systemic and biologic therapies, which underscores the use of risankizumab as a first- and secondary biologic agent.

These results highlight the clinical relevance of IL-23-blockers in contemporary psoriasis care and offer substantial clinical data about risankizumab as a reliable long-term care intervention. All in all, risankizumab can be considered a great milestone in terms of achieving long-lasting disease control and enhancing the quality of life of patients with moderate up to severe cases of plaque psoriasis.

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