Efficacy and Safety of Continuous Q12W Risankizumab versus Treatment Withdrawal: Results from the Phase 3 IMMhance Trial

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OBJECTIVE

- To evaluate the impact of risankizumab withdrawal on safety and maintenance of efficacy in patients with moderate-to-severe plaque psoriasis

INTRODUCTION

- Interleukin-23 (IL-23), a key regulator of multiple effector cytokines, plays a pivotal role in the development and maintenance of plaque psoriasis[1]
- The IL-23 inhibitor, risankizumab, demonstrated superior efficacy compared to placebo[2,3], ustekinumab[3], and adalimumab[4] at week 16
  - Maintained superior efficacy at week 52 compared with ustekinumab[3]
  - Demonstrated superior efficacy compared with adalimumab at Week 44, among subjects with partial response after 16-week treatment of adalimumab[4]

METHODS

- IMMhance is a Phase 3 confirmatory, multinational, multicenter, randomized, double-blinded, placebo-controlled study with randomized withdrawal and retreatment comparing risankizumab 150 mg dose with placebo
- In Part A1, patients were stratified by weight (≤100 kg vs >100 kg) and prior TNF inhibitor exposure, and then randomized 4:1 to receive 150 mg risankizumab (week 0 and 4) or placebo (**Figure 1**)
  - All patients received a 150 mg dose of risankizumab at Week 16
- In Part B, patients who initially received risankizumab and achieved sPGA 0/1 were stratified by weight (≤100 kg vs >100 kg) and prior TNF inhibitor exposure, and then randomized 1:2 to receive 150 mg risankizumab or placebo every 12 weeks (**Figure 1**)

KEY INCLUSION CRITERIA

- Adults with chronic moderate-to-severe plaque psoriasis for the past ≥6 months
- Stable plaque psoriasis defined as involved body surface area (BSA) ≥10%, Psoriasis Area and Severity Index (PASI) ≥12, and static Physician's Global Assessment (sPGA) ≥3
- Candidate for systemic therapy and phototherapy

KEY EXCLUSION CRITERIA

- Patients with non-plaque or drug-induced psoriasis
- Major surgery within 12 months prior to initial randomization or planned 12 months after screening
- Known chronic or relevant acute infection, such as HIV, viral hepatitis, or active tuberculosis
- Active or suspected malignancy, or history of malignancy within 5 years prior to screening
  - Except appropriately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ carcinoma of uterine cervix

ENDPOINTS

Efficacy Endpoint at Week 52:

Primary Efficacy Endpoint	• Achievement of sPGA score of clear or almost clear (0/1) at Week 52 among re-randomized patients

Additional Assessments:

Additional Analyses	• Achievement of PASI 90/100 at all visits collected • Achievement of sPGA 0/1 at all visits collected • Achievement of sPGA 0 at all visits collected • Time to sPGA ≥3 after re-randomization to either RZB or PBO
Safety Assessments	Treatment-emergent adverse events (TEAEs)*

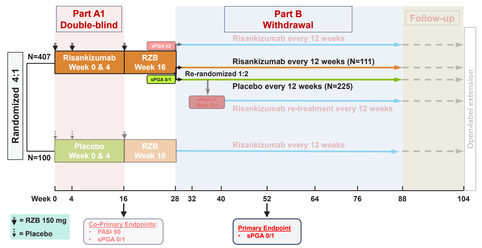
PASI, Psoriasis Area Severity Index; sPGA, static Physician's Global Assessment; RZB, risankizumab; PBO, placebo; TEAEs, treatment-emergent adverse events.
*Includes any adverse event (AE), serious AE, AE leading to drug discontinuation and other AEs of interest (major adverse cardiovascular events [MACE], serious infection, tuberculosis, fungal and opportunistic infections, malignancies, hypersensitivity reactions, and hepatic events).

METHODS (CONTINUED)

STATISTICAL ANALYSES

- Efficacy analyses in Part B were conducted on all patients re-randomized at week 28
  - Cochran-Mantel-Haenszel risk difference estimate stratified by baseline weight and prior TNFi exposure used for categorical variables
- The primary endpoint in Part B among re-randomized patients was tested independently from Part A endpoints
- Hierarchical testing procedure for endpoints used to control for multiplicity
- Missing efficacy data were imputed as non-responders for categorical variables
- Kaplan-Meier curve and log-rank test were used for time-to-event variables
- Safety analyses were conducted in all patients who received ≥1 dose of study drug

Figure 1. Study Design



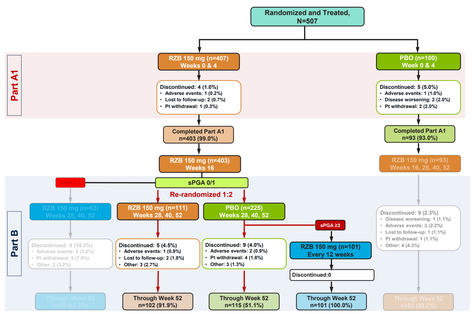
RZB, risankizumab; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.

RESULTS

- Patient disposition is presented in **Figure 2**
- Baseline patient demographics and disease characteristics were similar between the initially randomized treatment arms in Part A1 and re-randomized arms in Part B (week 28 onwards; **Table 1**)

PATIENTS

Figure 2. Patient Disposition[a]



RZB, risankizumab; PBO, placebo; sPGA, Physician's Global Assessment. [a]Discontinued indicates that patient discontinued study drug.

RESULTS (CONTINUED)

Table 1. Baseline Demographics and Disease Characteristics

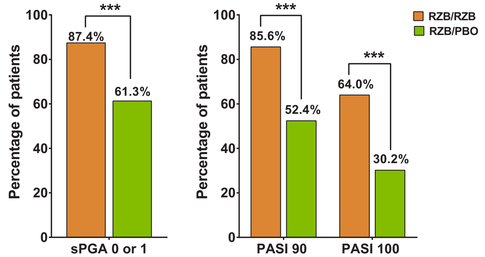
Characteristic	Part A1 (4:1) RZB N=407	Part A1 (4:1) PBO N=100	Part B (Re-randomization 1:2) RZB → RZB N=111	Part B (Re-randomization 1:2) RZB → PBO N=225
Age, years, median (range)	51 (19–79)	57 (19–80)	49 (19–74)	51 (21–79)
Male, n (%)	283 (70%)	73 (73%)	83 (75%)	156 (69%)
Race, White, n (%)	320 (79%)	82 (82%)	82 (74%)	177 (79%)
Weight, kg, median (range)	88.6 (47.0–193.1)	92.4 (51.7–137.3)	87.1 (47.0–164.3)	88.0 (47.2–159.4)
Weight >100 kg, n (%)[a]	124 (31%)	32 (32%)	32 (29%)	66 (29%)
BMI, kg/m^2, median (range)	30.0 (17.3–67.0)	30.9 (17.9–42.4)	29.6 (19.0–56.9)	30.0 (17.3–61.0)
PASI, median (range)	17.2 (12.0–63.4)	18.9 (12.0–54.2)	17.0 (12.0–63.4)	17.4 (12.0–47.6)
sPGA of severe, n (%)	84 (21%)	23 (23%)	25 (23%)	40 (18%)
BSA, %, median (range)	19 (10–90)	23 (10–90)	19 (10–90)	20 (10–84)
Prior non-biologic systemic therapy, n (%)	191 (47%)	42 (42%)	54 (49%)	106 (47%)
Any prior biologic therapy, n (%)	230 (57%)	51 (51%)	57 (51%)	125 (56%)
Prior TNFi, n (%)[a]	150 (37%)	35 (35%)	37 (33%)	75 (33%)
Prior non-TNFi, n (%)	168 (41%)	40 (40%)	41 (37%)	89 (40%)

[a]Stratification factors at randomization. BMI = Body Mass Index; BSA = Body Surface Area; PASI = Psoriasis Area and Severity Index; PBO = Placebo; RZB = Risankizumab; sPGA = static Physician's Global Assessment; TNFi = Tumor Necrosis Factor inhibitor.

EFFICACY

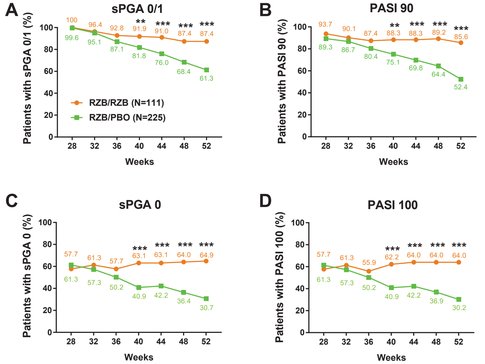
- The primary, other secondary, and further endpoints were achieved for risankizumab compared with withdrawal to placebo (week 52; *P*<.001; **Figures 3-4**)
- Median time to sPGA ≥3 was significantly different between patients re-randomized to continuous RZB (not determinable) compared with PBO (288 days) (*P*<.001; **Figure 5**)
- Median time to sPGA ≥3 was not determinable for continuous RZB since so few patients lost their response

Figure 3. Primary and Other Secondary Efficacy Endpoints at Week 52 (NRI)



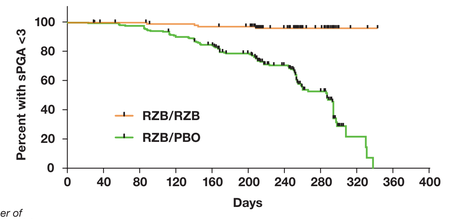
RZB, risankizumab; PBO, placebo; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; ***P<.001.

Figure 4. Time Courses for sPGA 0/1 (A), PASI 90 (B), sPGA 0 (C), and PASI 100 (D) Responses After Re-randomization



RZB, risankizumab; PBO, placebo; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; **P<.01; ***P<.001.

Figure 5. Time to sPGA ≥3 After Re-randomized to Either RZB or PBO



Number of patient at risk

RZB/RZB	111	109	108	105	103	99	72	32	2	0
RZB/PBO	225	223	219	203	187	164	108	49	3	0

RZB, risankizumab; PBO, placebo; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment. Dashes represents patients that were censored since they have no data beyond the indicated time point.

SAFETY

- Treatment-emergent adverse event (TEAE) were comparable across treatment groups at week 16 and in re-randomized arms from weeks 16 to 52 (**Table 2**)

Table 2. Treatment-Emergent Adverse Events

TEAEs, n (%)	Part A1 (4:1) RZB N=407	Part A1 (4:1) PBO N=100	Part B (Re-randomization 1:2) RZB → RZB N=111	Part B (Re-randomization 1:2) RZB → PBO N=225
Any AE	185 (45.5)	48 (48.0)	78 (70.3)	145 (64.4)
Drug related AEs[a]	33 (8.1)	7 (7.0)	15 (13.5)	20 (8.9)
Serious AE	8 (2.0)	8 (8.0)	7 (6.3)	14 (6.2)
Drug related serious AE[a]	0	1 (1.0)	1 (0.9)	1 (0.4)
Severe AE	6 (1.5)	4 (4.0)	5 (4.5)	13 (5.8)
AE leading to drug discontinuation	2 (0.5)	4 (4.0)	1 (0.9)	2 (0.9)
Infection[b]	69 (17)	18 (18.0)	53 (47.7)	89 (39.6)
Serious infection	0	1 (1.0)	2 (1.8)	2 (0.9)
Opportunistic infection	0	0	1 (0.9)	1 (0.4)
Active Tuberculosis[c]	0	0	0	0
Latent Tuberculosis	0	0	0	0
Serious hypersensitivity	0	0	0	0
Adjudicated MACE	0	1 (1.0)	1 (0.9)	0
Hepatic events	3 (0.7)	2 (2.0)	5 (4.5)	5 (2.2)
Malignancy	3 (0.7)	0	1 (0.9)	4 (1.8)
Malignancy excluding NMSC	2 (0.5)	0	1 (0.9)	3 (1.3)
AE leading to death	0	0	1 (0.9)[d]	0
Deaths (incl. non-treatment emergent)	0	0	1 (0.9)	0

[a]Investigator assessed AE as possibly related to study drug. [b]The most frequently reported infectious AE were viral upper respiratory tract infection and upper respiratory tract infection. [c]TB testing was performed at screening and at the end of treatment using QuantiFERON or PPD skin test. [d]One patient died on day 263 due an undetermined cause of death.
MACE, Major Adverse Cardiovascular Event; NMSC, Non-Melanoma Skin Cancer; RZB, Risankizumab; TEAEs, Treatment-Emergent adverse events.

CONCLUSIONS

- In patients with sPGA of clear or almost clear after 28 weeks risankizumab, statistically significantly larger proportion of patients with continuous treatment maintained sPGA 0/1 responses at Week 52.
- Similar results were also observed in other efficacy endpoints, including PASI 90, PASI 100, and sPGA 0. Starting at Week 40 (equivalent of a single missed dose), statistically significant differences were observed between patients re-randomized to continuous treatment and treatment withdrawal.
- Patients with continuous risankizumab treatment had significantly longer median time to relapse.
- Rates of treatment-emergent adverse events were similar to placebo at Week 16 and remained stable over time in patients treated with risankizumab.
- No additional safety concerns were identified in patients who were treated with risankizumab for 52 weeks compared with those who withdrew to placebo at week 28.

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