CLINICAL UPDATE

Brand Name	Skyrizi®
Generic Name	risankizumab-rzaa
Drug Manufacturer	Abbvie Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New Indication and Strength

FDA APPROVAL DATE

June 16, 2022

LAUNCH DATE

June 22, 2022

REVIEW DESIGNATION

N/A

TYPE OF REVIEW

Biologic License Application (BLA): 761105

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Skyrizi® is an interleukin-23 antagonist indicated for the treatment of:

- moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.
- active psoriatic arthritis in adults.
- moderately to severely active Crohn's disease in adults.

MECHANISMS OF ACTION

Risankizumab-rzaa is a humanized IgG1 monoclonal antibody that selectively binds to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses.

Risankizumab-rzaa inhibits the release of pro-inflammatory cytokines and chemokines.

DOSAGE FORM(S) AND STRENGTH(S)

Subcutaneous injection:

- Injection: 150 mg/mL in each single-dose prefilled pen
- Injection: 150 mg/mL in each single-dose prefilled syringe

- Injection: 75 mg/0.83 mL in each single-dose prefilled syringe.
- Injection: 360 mg/2.4 mL (150 mg/mL) in each single-dose prefilled cartridge

Intravenous infusion:

- Injection: 600 mg/10 mL (60 mg/mL) in each single-dose vial.

DOSE & ADMINISTRATION

- For the treatment of Crohn's disease, obtain liver enzymes and bilirubin levels prior to initiating treatment with Skyrizi®.
- Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with Skyrizi®.
- Complete all age-appropriate vaccinations as recommended by current immunization guidelines.

Plaque Psoriasis: 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

Psoriatic Arthritis: 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

EFFICACY

Plaque Psoriasis:

Four multicenter, randomized, double-blind studies [PsO-1 (NCT02684370), PsO-2 (NCT02684357), PsO-3 (NCT02672852), and PsO-4 (NCT02694523)] enrolled 2109 subjects 18 years of age and older with moderate to severe plaque psoriasis who had a body surface area (BSA) involvement of ≥10%, a static Physician's Global Assessment (sPGA) score of ≥3 ("moderate") in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 4, and a Psoriasis Area and Severity Index (PASI) score ≥12.

Overall, subjects had a median baseline PASI score of 17.8 and a median BSA of 20%. Baseline sPGA score was 4 ("severe") in 19% of subjects. A total of 10% of study subjects had a history of diagnosed psoriatic arthritis.

Across all studies, 38% of subjects had received prior phototherapy, 48% had received prior nonbiologic systemic therapy, and 42% had received prior biologic therapy for the treatment of psoriasis.

Studies PsO-1 and PsO-2

In studies PsO-1 and PsO-2, 997 subjects were enrolled (including 598 subjects randomized to the Skyrizi® 150 mg group, 200 subjects randomized to the placebo group, and 199 to the biologic active control group). Subjects received treatment at Weeks 0, 4, and every 12 weeks thereafter.

Both studies assessed the responses at Week 16 compared with placebo for the two co-primary endpoints:

- the proportion of subjects who achieved an sPGA score of 0 ("clear") or 1 ("almost clear").
- the proportion of subjects who achieved at least a 90% reduction from baseline PASI (PASI 90).

Secondary endpoints included the proportion of subjects who achieved PASI 100, sPGA 0, and Psoriasis Symptom Scale (PSS) 0 at Week 16. The results are presented in Table 1.

Table 1. Efficacy results at week 16 in adults with Plaque Psoriasis in PSO-1 AND PSO-2

	PsO-1		PsO-2	
	Skyrizi® (N=304) n (%)	**Placebo (N=102) n (%)**	**Skyrizi® (N=294) n (%)**	**Placebo (N=98) n (%)**

sPGA 0 or 1 ("clear or almost clear") [a]	267 (88)	8 (8)	246 (84)	5 (5)
PASI 90[a]	229 (75)	5 (5)	220 (75)	2 (2)
sPGA 0 ("clear")	112 (37)	2 (2)	150 (51)	3 (3)
PASI 100	109 (36)	0 (0)	149 (51)	2 (2)
[a] Co-primary endpoint				

Examination of age, gender, race, body weight, baseline PASI score and previous treatment with systemic or biologic agents did not identify differences in response to Skyrizi® among these subgroups at Week 16.

In PsO-1 and PsO-2 at Week 52, subjects receiving Skyrizi® achieved sPGA 0 (58% and 60%, respectively), PASI 90 (82% and 81%, respectively), and PASI 100 (56% and 60%, respectively).

Patient Reported Outcomes: Improvements in signs and symptoms related to pain, redness, itching and burning at Week 16 compared to placebo were observed in both studies as assessed by the PSS. In PsO-1 and PsO-2, about 30% of the subjects who received Skyrizi® achieved PSS 0 ("none") at Week 16 compared to 1% of the subjects who received placebo.

Study PsO-3

Study PsO-3 enrolled 507 subjects (407 randomized to Skyrizi® 150 mg and 100 to placebo). Subjects received treatment at Weeks 0, 4, and every 12 weeks thereafter.

At Week 16, Skyrizi® was superior to placebo on the co-primary endpoints of sPGA 0 or 1 (84% Skyrizi® and 7% placebo) and PASI 90 (73% Skyrizi® and 2% placebo). The respective response rates for Skyrizi® and placebo at Week 16 were: sPGA 0 (46% Skyrizi® and 1% placebo); PASI 100 (47% Skyrizi® and 1% placebo); and PASI 75 (89% Skyrizi® and 8% placebo).

Maintenance and Durability of Response

In PsO-1 and PsO-2, among the subjects who received Skyrizi® and had PASI 100 at Week 16, 80% (206/258) of the subjects who continued on Skyrizi® had PASI 100 at Week 52. For PASI 90 responders at Week 16, 88% (398/450) of the subjects had PASI 90 at Week 52.

In PsO-3, subjects who were originally on Skyrizi® and had sPGA 0 or 1 at Week 28 were rerandomized to continue Skyrizi® every 12 weeks or withdrawal of therapy. At Week 52, 87% (97/111) of the subjects re-randomized to continue treatment with Skyrizi® had sPGA 0 or 1 compared to 61% (138/225) who were re-randomized to withdrawal of Skyrizi®.

Psoriatic Arthritis:

The safety and efficacy of Skyrizi® were assessed in 1407 subjects in 2 randomized, double blind, placebo-controlled studies (964 in PsA-1 [NCT03675308] and 443 in PsA-2 [NCT03671148]) in subjects 18 years and older with active psoriatic arthritis (PsA).

Subjects in these studies had a diagnosis of PsA for at least 6 months based on the Classification Criteria for Psoriatic Arthritis (CASPAR), a median duration of PsA of 4.9 years at baseline, ≥ 5 tender joints and ≥ 5 swollen joints, and active plaque psoriasis or psoriatic nail disease at baseline. Regarding baseline clinical presentation, 55.9% of subjects had ≥3% BSA with active plaque psoriasis; 63.4% and 27.9% of subjects had enthesitis and dactylitis, respectively. In PsA1 where psoriatic nail disease was further assessed, 67.3% had psoriatic nail disease.

In PsA-1, all subjects had a previous inadequate response or intolerance to non-biologic DMARD therapy and were biologic naïve. In PsA-2, 53.5% of subjects had a previous inadequate response or intolerance to non-biologic DMARD therapy, and 46.5% of subjects had a previous inadequate response or intolerance to biologic therapy.

In both studies, subjects were randomized to receive Skyrizi® 150 mg or placebo at Weeks 0, 4, and 16. Starting from Week 28, all subjects received Skyrizi® every 12 weeks. Both studies included a long-term extension for up to an additional 204 weeks. Regarding use of concomitant medications, 59.6% of subjects were receiving concomitant methotrexate (MTX), 11.6% were receiving concomitant non-biologic DMARDs other than MTX, and 28.9% were receiving Skyrizi® monotherapy.

For both studies, the primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response at Week 24.

Clinical Response

In both studies, treatment with Skyrizi® resulted in significant improvement in measures of disease activity compared with placebo at Week 24. See Tables 2 and 3 for key efficacy results.

In both studies, similar responses were seen regardless of concomitant non-biologic DMARD use, number of prior non-biologic DMARDs, age, gender, race, and BMI. In PsA-2, responses were seen regardless of prior biologic therapy.

Table 2. Efficacy Results in Study PsA-1

Endpoint	Placebo N=481 Response Rate	Skyrizi® N=483 Response Rate	Difference from Placebo (95% CI)
ACR20 Response*			
Week 16	33.4%	56.3%[a]	23.1% (16.8, 29.4)
Week 24	33.5%	57.3%[a]	24.0% (18.0, 30.0)
ACR50 Response*			
Week 16	11.1%	26.4%	15.4% (10.6, 20.2)
Week 24	11.3%	33.4%	22.2% (17.3, 27.2)
ACR70 Response*			
Week 16	2.7%	11.8%	9.2% (6.1, 12.4)
Week 24	4.7%	15.3%	10.5% (6.9, 14.2)

a. multiplicity-controlled p≤0.001, Skyrizi® vs. placebo comparison.

*A Subject was considered as a non-responder after initiation of rescue medication or concomitant medications for PsA that could meaningfully impact efficacy assessment.

Table 3. Efficacy Results in Study PsA-2

Endpoint	Placebo N=219 Response Rate	Skyrizi® N=224 Response Rate	Difference from Placebo (95% CI)
ACR20 Response*			
Week 16	25.3%	48.3% [a]	22.6% (13.9, 31.2)
Week 24	26.5%	51.3% [a]	24.5% (15.9, 33.0)
ACR50 Response*			
Week 16	6.8%	20.3%	13.5% (7.3, 19.7)
Week 24	9.3%	26.3%	16.6% (9.7, 23.6)
ACR70 Response*			

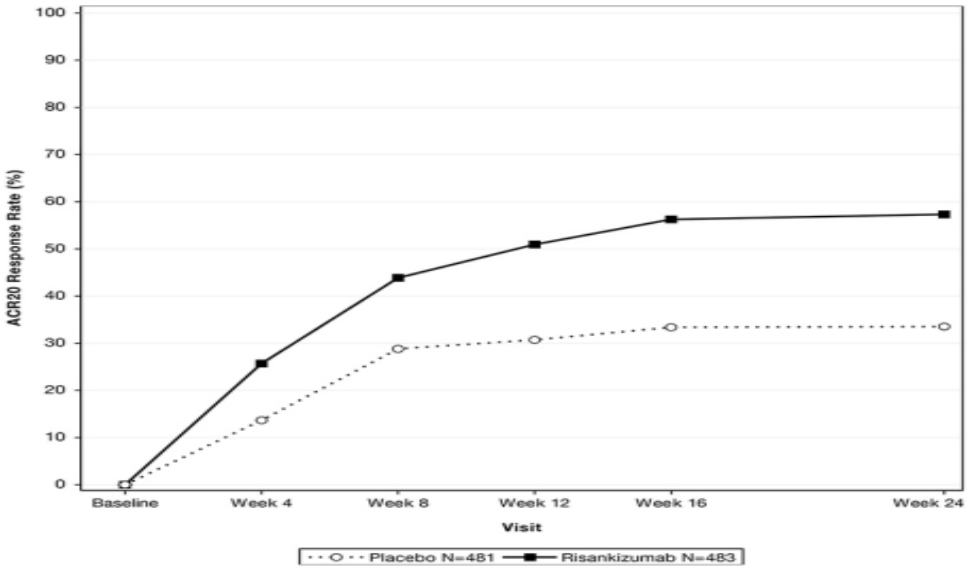
Week 16	3.4%	11.2%	7.8% (3.0, 12.6)
Week 24	5.9%	12.0%	6.0% (0.8, 11.3)

a. multiplicity-controlled p≤0.001, Skyrizi® vs. placebo comparison.

*A Subject was considered as a non-responder after initiation of rescue medication or concomitant medications for PsA that could meaningfully impact efficacy assessment.

The percent of subjects achieving ACR20 responses in study PsA-1 through Week 24 is shown in Figure 1.

Figure 1. Percent of Subjects Achieving ACR20 Responses in Study PsA-1 through Week 24



The results of the components of the ACR response criteria for both studies are shown in Table 4.

Table 4. Mean Change from Baseline in ACR Components

	PsA-1		PsA-2	
	Placebo (N=481) Mean (SD)	Skyrizi® (N=483) Mean (SD)	Placebo (N=219) Mean (SD)	Skyrizi® (N=224) Mean (SD)
Number of Swollen Joints (0-66)				
Baseline	12.2 (8.0)	12.1 (7.8)	13.6 (9.0)	13.0 (8.7)
Mean change at Week 16	-5.5 (7.0)	-7.7 (7.2)	-5.4 (8.5)	-8.0 (7.4)
Mean change at Week 24	-6.7 (7.2)	-8.7 (7.2)	-6.5 (7.8)	-9.1 (7.6)
Number of Tender Joints (0-68)				
Baseline	20.5 (12.8)	20.8 (14.0)	22.3 (13.8)	22.8 (14.9)
Mean change at Week 16	-6.3 (11.1)	-10.7 (11.4)	-6.0 (13.1)	-11.3 (13.0)
Mean change at Week 24	-7.9 (10.7)	-12.0 (12.3)	-8.3 (11.3)	-13.0(12.5)
Patient's Assessment of Pain [a]				
Baseline	57.1 (22.6)	57.1 (22.6)	57.0 (23.1)	55.0 (23.5)
Mean change at Week 16	-8.6 (23.7)	-18.4 (26.3)	-5.7 (22.7)	-14.4 (26.4)
Mean change at Week 24	-10.9 (25.4)	-21.4 (26.5)	-8.7 (25.3)	-15.3 (26.5)
Patient's Global Assessment [a]				
Baseline	57.4 (22.1)	57.9 (21.7)	56.2 (23.0)	56.2 (21.8)
Mean change at Week 16	-10.2 (23.9)	-19.4 (25.7)	-4.9 (23.6)	-17.0 (27.1)

Mean change at Week 24	-11.1 (25.1)	-22.6 (26.9)	-8.7 (25.4)	-17.7 (27.7)
Physician Global Assessment [a]				
Baseline	62.4 (17.0)	61.3 (17.6)	60.7 (16.4)	63.0 (17.0)
Mean change at Week 16	-18.3 (22.5)	-31.1 (23.4)	-19.0 (23.3)	-32.7 (24.7)
Mean change at Week 24	-22.2 (22.8)	-34.8 (23.2)	-21.3 (25.2)	-35.5 (25.6)
Health Assessment Questionnaire - Disability Index (HAQ-DI) [b]				
Baseline	1.2 (0.7)	1.2 (0.7)	1.1 (0.6)	1.1 (0.6)
Mean change at Week 16	-0.1 (0.5)	-0.3 (0.5)	-0.1 (0.5)	-0.2 (0.5)
Mean change at Week 24	-0.1 (0.5)	-0.3 (0.5)	-0.1 (0.4)	-0.2 (0.5)
High sensitivity C-reactive protein (hs-CRP) mg/L				
Baseline	11.3 (14.1)	11.9 (15.9)	8.2 (17.1)	7.4 (10.9)
Mean change at Week 16	-0.3 (14.7)	-4.8 (14.2)	-0.1 (6.8)	-2.1 (7.5)
Mean change at Week 24	-0.2 (11.7)	-4.3 (12.8)	-0.5 (14.5)	-1.8 (13.4)

SD= Standard Deviation.

a. Assessment based on Visual Analog Scale (100 mm) with the left end indicating "no pain" (for patient's assessment of pain), "very well" (for patient global assessment), or "no arthritis activity" (for physician global assessment) and the right end indicating "the worst possible pain" (for patient assessment of pain), "poor" (for patient global assessment), or "extremely active arthritis" (for physician global assessment).

b. Disability Index of the Health Assessment Questionnaire; 0 = no difficulty to 3 = inability to perform, measures the patient's ability to perform the following: dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living.

Treatment with Skyrizi® resulted in improvement in dactylitis and enthesitis in subjects with pre-existing dactylitis or enthesitis.

In patients with coexistent plaque psoriasis receiving Skyrizi®, the skin lesions of psoriasis improved with treatment, relative to placebo, as measured by the Psoriasis Area Severity Index (PASI 90) at Week 24.

Physical Function

In both studies, patients treated with Skyrizi® showed statistically significant improvement from baseline in physical function compared with placebo as assessed by HAQ-DI at Week 24 (Table 4). The mean difference (95% CI) from placebo in HAQ-DI change from baseline at Week 24 was -0.20 (-0.26, -0.14) in study PsA-1 and -0.16 (-0.26, -0.07) in study PsA-2.

In both studies, a greater proportion of subjects achieved a reduction of at least 0.35 in HAQ-DI score from baseline in the Skyrizi® group compared with placebo at Week 24.

Other Health Related Outcomes

In both studies, general health status was assessed by the 36-Item Short Form Health Survey (SF36 V2). Fatigue was assessed by Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue).

In both studies at Week 24, subjects treated with Skyrizi® showed improvements in the SF-36 physical component summary scores compared with subjects who received placebo. There were also numerical improvements in subjects treated with Skyrizi® in physical functioning, role physical, bodily pain, general health, vitality, social functioning, mental health, role emotional domain scores and mental component summary scores in both studies at week 24 compared to placebo. In both studies at Week 24, subjects treated with Skyrizi® showed improvements in FACIT-Fatigue scores compared with subjects who received placebo.

Crohn's Disease:

Induction Trials (Studies CD-1 and CD-2)

n two 12-week induction studies (CD-1; NCT03105128 and CD-2; NCT03104413), subjects with moderately to severely active Crohn's disease were randomized to receive Skyrizi® 600 mg, Skyrizi® 1,200 mg, or placebo as an intravenous infusion at Week 0, Week 4, and Week 8. Moderately to severely active CD was defined as a Crohn's Disease Activity Index (CDAI) of 220 to 450 and Simple Endoscopic Score for Crohn's disease (SES-CD) ≥6 (or ≥4 for isolated ileal disease). Subjects with inadequate response, loss of response, or intolerance to oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapy were enrolled.

At baseline, the median CDAI was 307 (range: 76 – 634) and 307 (range: 72 – 651), and the median SES-CD was 12 (range: 4 – 45) and 13 (range 4 – 40), in CD-1 and CD-2, respectively. In CD-1, 58% (491/850) of subjects had failed or were intolerant to treatment with one or more biologic therapies (prior biologic failure). All subjects in CD-2 had prior biologic failure. At baseline, 30% and 34% of patients were receiving corticosteroids, 24% and 23% of patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and 31% and 19% of patients were receiving aminosalicylates in CD-1 and CD-2, respectively. In CD-1 and CD-2 combined, the median age was 36 years (ranging from 16 to 80 years), 81% (1145/1419) of subjects were white, and 53% (753/1419) were male.

In CD-1 and CD-2, the co-primary endpoints were clinical remission and endoscopic response at Week 12. Secondary endpoints included clinical response and endoscopic remission (see Table 5 and Table 6). The Skyrizi® 1,200 mg dosage did not demonstrate additional treatment benefit over the 600 mg dosage and is not a recommended regimen.

Table 5. Proportion of Subjects Meeting Efficacy Endpoints at Week 12 – Study CD-1

Endpoint	Placebo	Skyrizi® 600 mg Intravenous Infusion[a]	Treatment Difference [b] (95% CI)
Clinical Remission[c,d]			
Total Population	N=175 25%	N=336 45%	**21% [e] (12%, 29%)**
Prior biologic failure[f]	N=97 26%	N=195 42%	
Without prior biologic failure	N=78 23%	N=141 49%	
Endoscopic Response[c,g]			
Total Population	N=175 12%	N=336 40%	**28% [e] (21%, 35%)**
Prior biologic failure[f]	N=97 11%	N=195 33%	
Without prior biologic failure	N=78 13%	N=141 50%	
Clinical Response[h]			
Total Population	N=175 37%	N=336 60%	**23% [e] (14%, 32%)**
Prior biologic failure[f]	N=97 34%	N=195 58%	
Without prior biologic failure	N=78 40%	N=141 62%	
Endoscopic Remission[i]			
Total Population	N=175 9%	N=336 24%	**15% [e] (9%, 21%)**
Prior biologic failure[f]	N=97 5%	N=195 18%	
Without prior biologic failure	N=78 14%	N=141 32%	

a. All subjects enrolled in CD-2 had prior biologic failure. Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologic treatments for CD.
b. Skyrizi® 600 mg as an intravenous infusion at Week 0, Week 4, and Week 8
c. Adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors.
d. Co-primary endpoints
e. CDAI <150
f. p <0.001
g. A decrease in SES-CD > 50% from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease, based on central reading
h. A reduction of CDAI ≥ 100 points from baseline
i. SES-CD ≤ 4 and at least a 2-point reduction from baseline, with no individual sub score greater than 1, based on central reading.

Table 6. Proportion of Subjects Meeting Efficacy Endpoints at Week 12 – Study CD-2[a]

Endpoint	Placebo N=187	Skyrizi® 600 mg Intravenous Infusion[b] N=191	Treatment Difference[c] (95% CI)
Clinical Remission[d,e]	20%	42%	22% [f] (13%, 31%)
Endoscopic Response [d,g]	11%	29%	18% [f] (10%, 25%)
Clinical Response[h]	30%	60%	29% [f] (20%, 39%)
Endoscopic Remission[i]	4%	19%	15% [f] (9%, 21%)

a. All subjects enrolled in CD-2 had prior biologic failure. Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologic treatments for CD
b. Skyrizi® 600 mg as an intravenous infusion at Week 0, Week 4, and Week 8
c. Adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors
d. Co-primary endpoints
e. CDAI score <150
f. p < 0.001
g. A decrease in SES-CD > 50% from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease, based on central reading h. A reduction of CDAI ≥ 100 points from baseline
h. SES-CD ≤ 4 and at least a 2-point reduction versus from baseline, with and no individual subscore greater than 1, based on central reading

Onset of clinical response and clinical remission based on CDAI occurred as early as Week 4 in a greater proportion of subjects treated with the Skyrizi® 600 mg induction regimen compared to placebo.

Reductions in stool frequency and abdominal pain were observed in a greater proportion of subjects treated with the Skyrizi® 600 mg induction regimen compared to placebo.

Study CD-3

The maintenance study CD-3 evaluated 247 subjects who achieved clinical response defined as a reduction in CDAI of at least 100 points from baseline after 12 weeks of induction treatment with intravenous Skyrizi® in studies CD-1

and CD-2. Subjects were randomized to receive a maintenance regimen of Skyrizi® 360 mg or placebo at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks.

The co-primary endpoints in CD-3 were clinical remission and endoscopic response at Week 52 (see Table 7).

Table 7. Proportion of Subjects Meeting Efficacy Endpoints at Week 52 - Study CD-3

Endpoint	Placebo[a]	Skyrizi® 360 mg Subcutaneous Injection[b]	Treatment Differencevs Placebo[c] (95% CI)
Clinical Remission[d,e]			
Total Population	N=130 46%	N=117 57%	14% [f] (3%, 26%)
Prior biologic failure[g]	N=99 40%	N=83 51%	
Without prior biologic failure	N=31 65%	N=34 71%	
Endoscopic Response[d,h]			
Total Population	N=130 22%	N=117 48%	31% [f] (21%, 41%)
Prior biologic failure[g]	N=99 21%	N=83 44%	
Without prior biologic failure	N=31 23%	N=34 59%	

a. The placebo group consisted of patients who were in response to Skyrizi® and were randomized to receive placebo at the start of maintenance therapy.
b. Skyrizi® 360 mg at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks
c. Adjusted treatment difference and 95% CI computed using Cochran-Mantel-Haenszel method adjusted for randomization stratification factors.
d. Co-primary endpoints
e. CDAI <150
f. p <0.05
g. Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologic treatments for CD
h. A decrease in SES-CD > 50% from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease, based on central reading.

Endoscopic remission was observed at Week 52 in 41% (48/117) of subjects treated with the Skyrizi® maintenance regimen and 13% (17/130) of subjects treated with placebo. This endpoint was not statistically significant under the prespecified multiple testing procedure.