

Icotrokinra, a targeted oral peptide that selectively blocks IL-23 receptor activation, in moderately to severely active ulcerative colitis: Week 12 results from the Phase 2b, randomized, double-blind, placebo-controlled, treat-through, dose-ranging ANTHEM-UC trial

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Disclosure of Conflicts of Interest

I, **Vipul Jairath**, herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Consulting fees from Abbvie, Alimentiv, Amgen, Anaptys Bio, Asahi Kasei, Asieris, Astra Zeneca, Attovia, Blackbird Labs, BMS, Boehringer Ingleheim, Biomebank, Caldera, Calluna, Catalytic Health, Celltrion, Ensho, Entera, Exeliome Biosciences, Ferring, Fresenius Kabi, Gilead, Granite Bio, GSK, Janssen, Lilly, Merck, Mountainfield, MRM Health, Nxera, Organon, OSE Immunotherapeutics, Pendopharm, Pioneering Medicine, Pfizer, Prometheus, Roche/Genentech, Sanofi, SCOPE, Shattuck Labs, Sorriso, Spyre, Synedgen, Takeda, Teva, Tillotts, Union Therapeutics, Ventus, Ventyx, Vividion, Xencor, Zealand Pharma.

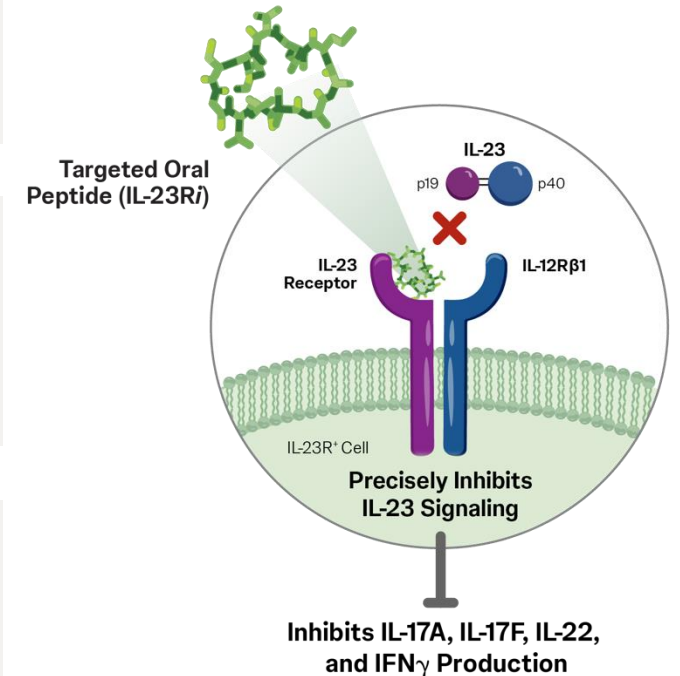
Background and Objective

Despite the availability of advanced therapeutic options, there remains an unmet need for an efficacious oral drug with a favorable safety profile for the management of ulcerative colitis

IL-23 plays a central role in the pathogenesis of ulcerative colitis, and inhibition of IL-23 by monoclonal antibodies is a safe and highly effective treatment option for patients with IBD

Icotrokinra (formerly JNJ-2113) is a first-in-class targeted oral peptide that potently and selectively blocks the IL-23 receptor at the site of inflammation

Icotrokinra Blocks IL-23 From Binding to its Receptor



Background and Objective

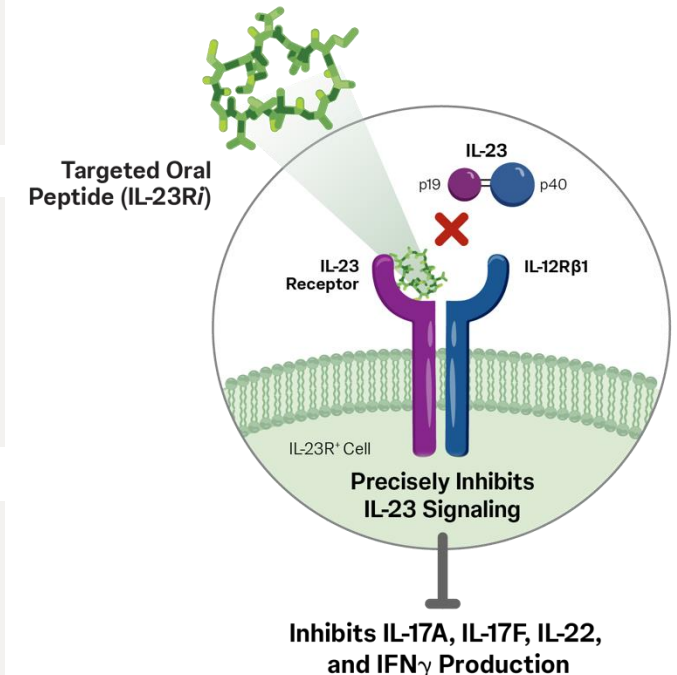
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ANTHEM-UC (NCT06049017) evaluated the efficacy and safety of three doses of once-daily oral icotrokinra in adult participants with moderately to severely active ulcerative colitis

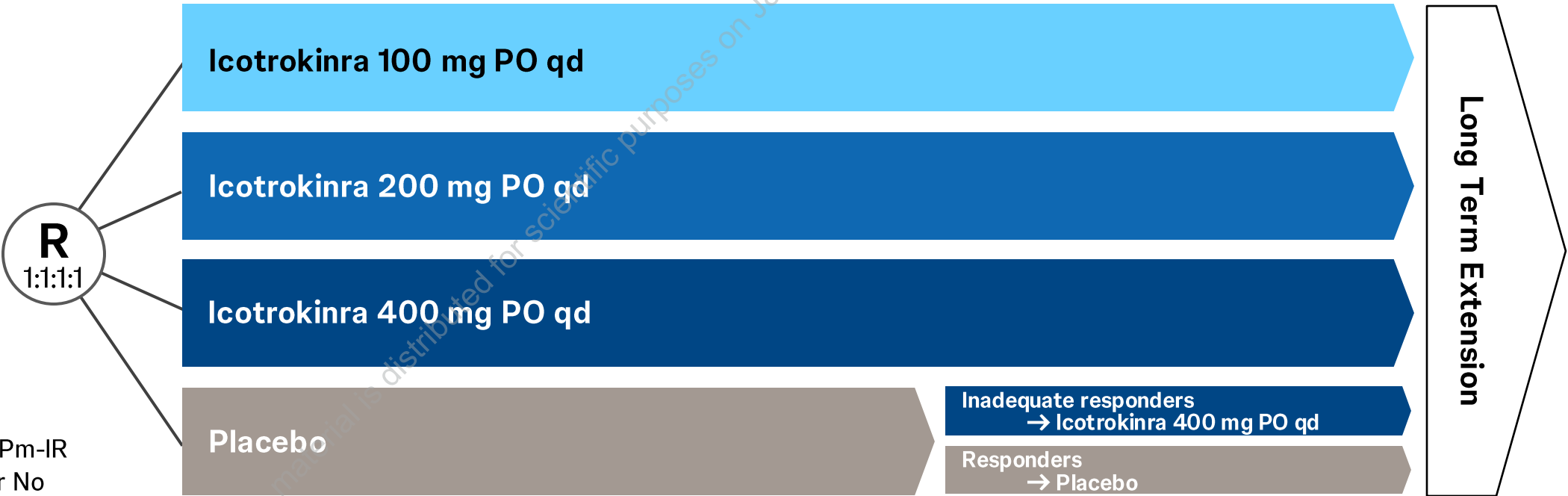
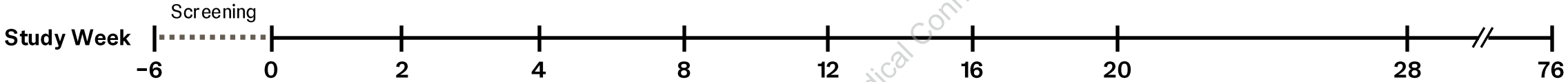
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ANTHEM-UC Study Design

Key Eligibility Criteria

- Diagnosed ulcerative colitis of ≥ 12 weeks duration and a Modified Mayo score (mMS) of 5–9, inclusive
- Mayo endoscopic subscore (MES) ≥ 2 per central review of screening video endoscopy
- Inadequate response/intolerance (IR) to corticosteroids, 6-MP, or AZA **OR** corticosteroid dependence **OR** IR to TNF α antagonists, ustekinumab, vedolizumab, JAK inhibitors, or S1P modulators (BIO/JAKi/S1Pm-IR)



Stratification

- BIO/JAKi/S1Pm-IR status: Yes or No
- Baseline MES: 2 or 3

Testing Procedure and Statistical Considerations

Primary Endpoint:

- Clinical response vs placebo at Week 12

Secondary Endpoints (all vs placebo at Week 12)

- Clinical remission
- Symptomatic remission
- Endoscopic improvement
- Histologic-endoscopic mucosal improvement (HEMI)

- ✓ The study was powered to detect a treatment difference between icotrokinra 400 mg and placebo for the primary endpoint; it was not powered for the secondary endpoints
- ✓ Statistical testing was conducted sequentially: if a comparison was $p \geq 0.05$, all subsequent comparisons were not significant and nominal p-values are presented

Demographics and Baseline Disease Characteristics

	Placebo	Icotrokinra 100 mg qd	Icotrokinra 200 mg qd	Icotrokinra 400 mg qd	Total
Full analysis set, n	63	64	62	63	252
Age, years, mean (SD)	38.3 (13.8)	45.8 (14.6)	41.8 (14.6)	40.6 (14.8)	41.6 (14.7)
Sex, male, n (%)	35 (55.6%)	40 (62.5%)	32 (51.6%)	40 (63.5%)	147 (58.3%)
Race, White, n (%)	44 (69.8%)	45 (70.3%)	39 (62.9%)	42 (66.7%)	170 (67.5%)
UC disease duration, years, mean (SD)	8.3 (8.1)	7.4 (6.1)	7.8 (7.5)	7.6 (7.6)	7.8 (7.3)
Extensive disease, n (%)	27 (42.9%)	23 (35.9%)	23 (37.1%)	29 (46.0%)	102 (40.5%)
Modified Mayo score [max = 9], mean (SD)	6.75 (1.231)	6.55 (1.296)	6.75 (1.386)	6.49 (1.401)	6.63 (1.327)
Mayo endoscopic subscore of 3 (severe), n (%)	36 (57.1%)	38 (59.4%)	37 (59.7%)	37 (58.7%)	148 (58.7%)
Fecal calprotectin, mg/kg, median [IQR]	1467.0 [420.5; 3622.0]	1433.3 [698.0; 3121.2]	2467.0 [646.4; 4599.6]	1421.3 [584.6; 4978.6]	1523.0 [587.0; 3816.7]
CRP, mg/L, median [IQR]	3.0 [0.9; 7.0]	3.0 [1.1; 6.7]	5.3 [1.5; 11.3]	4.0 [1.5; 8.1]	3.6 [1.3; 8.1]

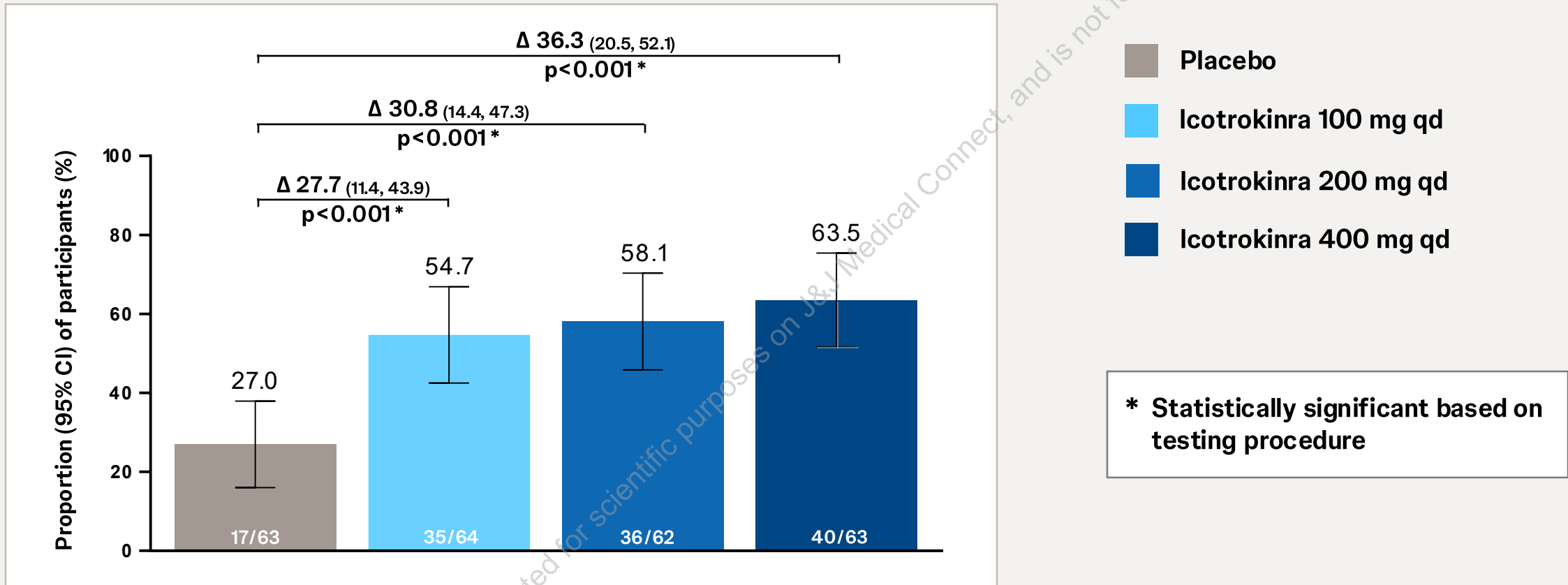
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Baseline Medications for Ulcerative Colitis

	Placebo	lctrokinra 100 mg qd	lctrokinra 200 mg qd	lctrokinra 400 mg qd	Total
Full analysis set, n	63	64	62	63	252
Baseline corticosteroid use, n (%)	21 (33.3%)	21 (32.8%)	29 (46.8%)	23 (36.5%)	94 (37.3%)
Baseline immunomodulator use, n (%)	16 (25.4%)	10 (15.6%)	10 (16.1%)	6 (9.5%)	42 (16.7%)
No history of BIO/JAKi/S1Pm-IR, n (%)	35 (55.6%)	38 (59.4%)	36 (58.1%)	34 (54.0%)	143 (56.7%)
BIO/JAKi/S1Pm-IR, n (%)	28 (44.4%)	26 (40.6%)	26 (41.9%)	29 (46.0%)	109 (43.3%)
IR to 1 class / mechanism^a	22 (78.6%)	19 (73.1%)	21 (80.8%)	15 (51.7%)	77 (70.6%)
IR to 2 classes / mechanisms^a	6 (21.4%)	6 (23.1%)	5 (19.2%)	14 (48.3%)	31 (28.4%)
IR to >2 classes / mechanisms^a	0	1 (3.8%)	0	0	1 (0.9%)

a. Denominator was number of participants with a history of inadequate response or intolerance to biologics, JAK inhibitors, or S1P modulators (BIO/JAKi/S1Pm-IR)
 BIO = TNF α antagonists, ustekinumab, or vedolizumab; IR = prior inadequate response or intolerance.

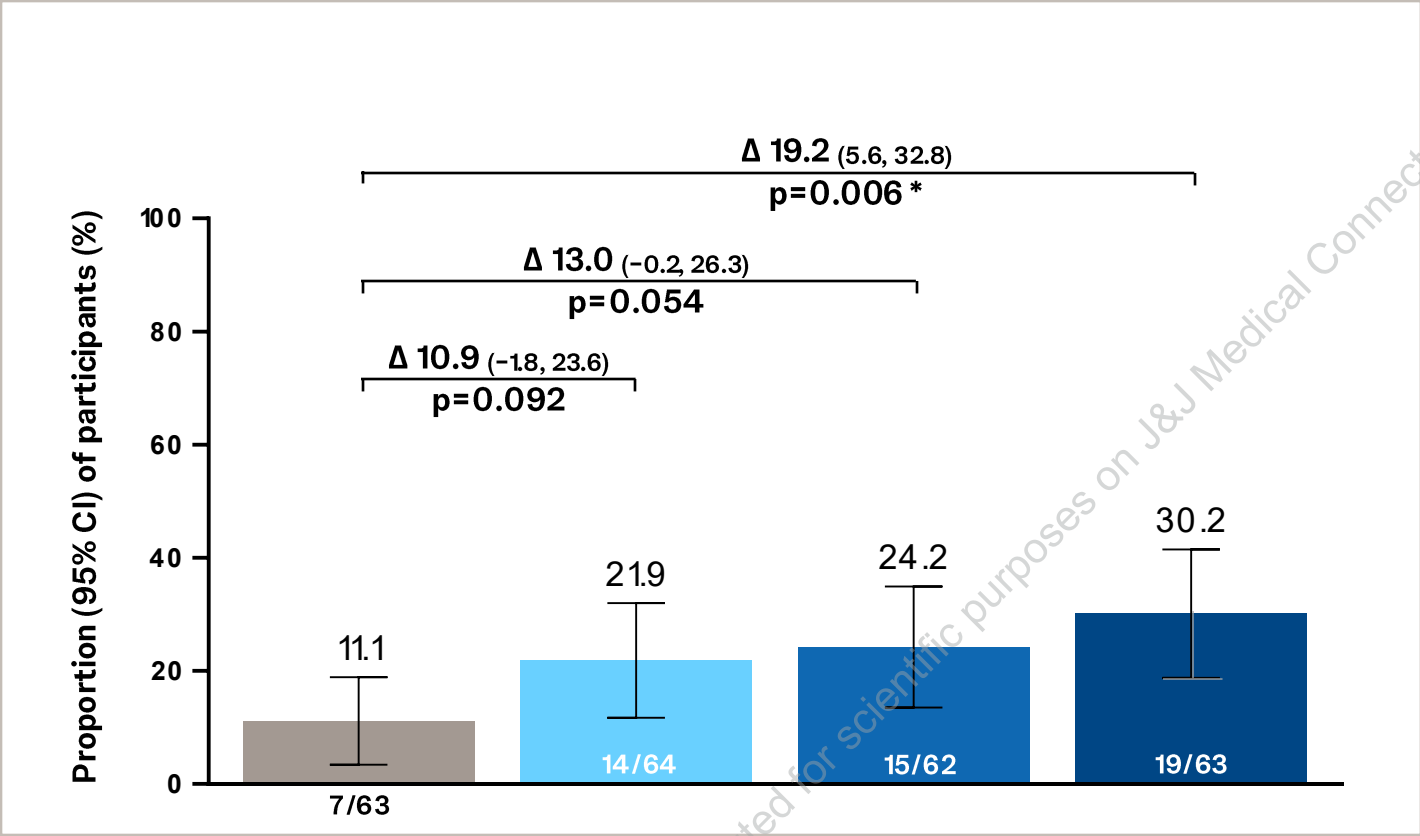
Primary Endpoint: Clinical Response at Week 12



Clinical response: a decrease from baseline in the modified Mayo score by $\geq 30\%$ and ≥ 2 points, with either a ≥ 1 -point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/ JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopic subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Clinical Remission at Week 12



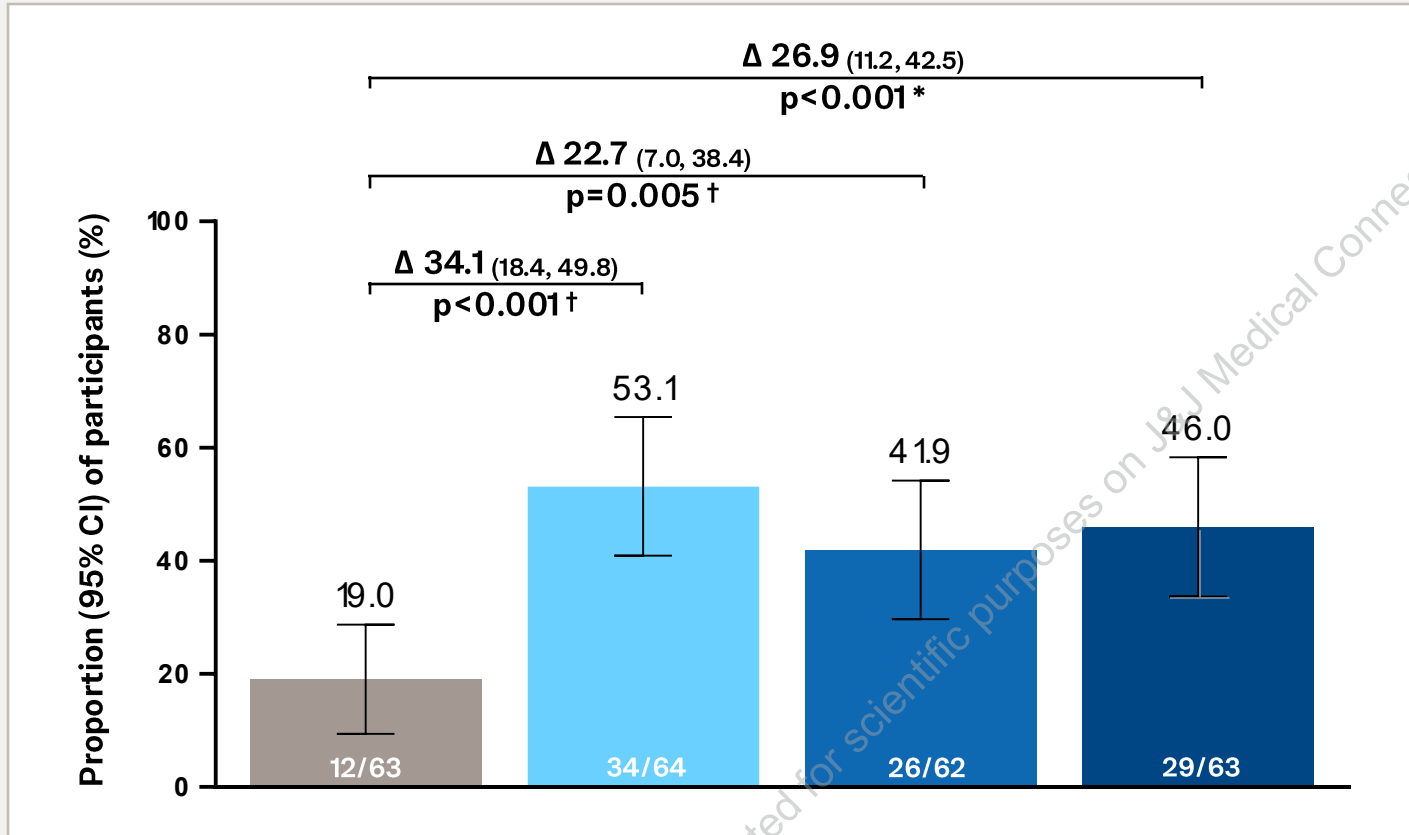
- Placebo
- Icotrokinra 100 mg qd
- Icotrokinra 200 mg qd
- Icotrokinra 400 mg qd

*** Statistically significant based on testing procedure**

Clinical remission: stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and Mayo endoscopic subscore of 0 or 1

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/ JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopic subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Symptomatic Remission at Week 12



- Placebo
- Icotrokinra 100 mg qd
- Icotrokinra 200 mg qd
- Icotrokinra 400 mg qd

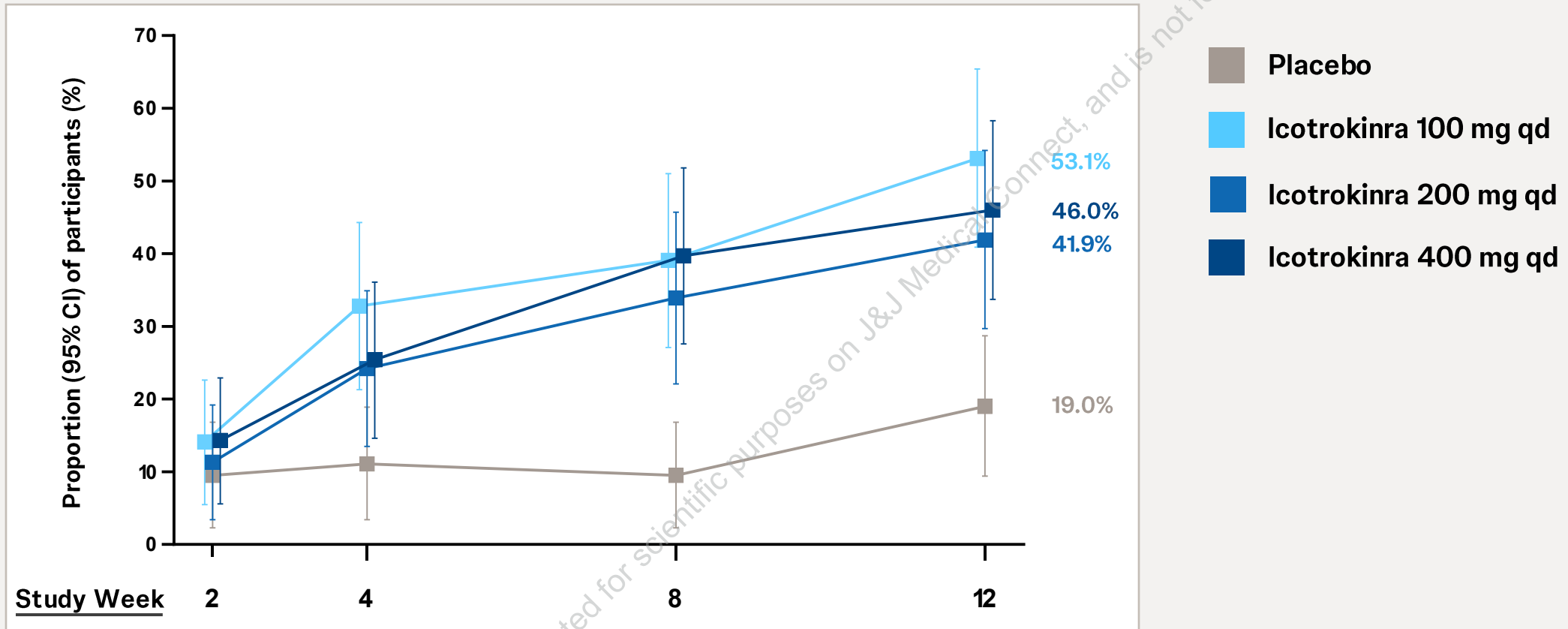
* Statistically significant based on testing procedure

† Nominal p-value < 0.05

Symptomatic remission: stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/ JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopic subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

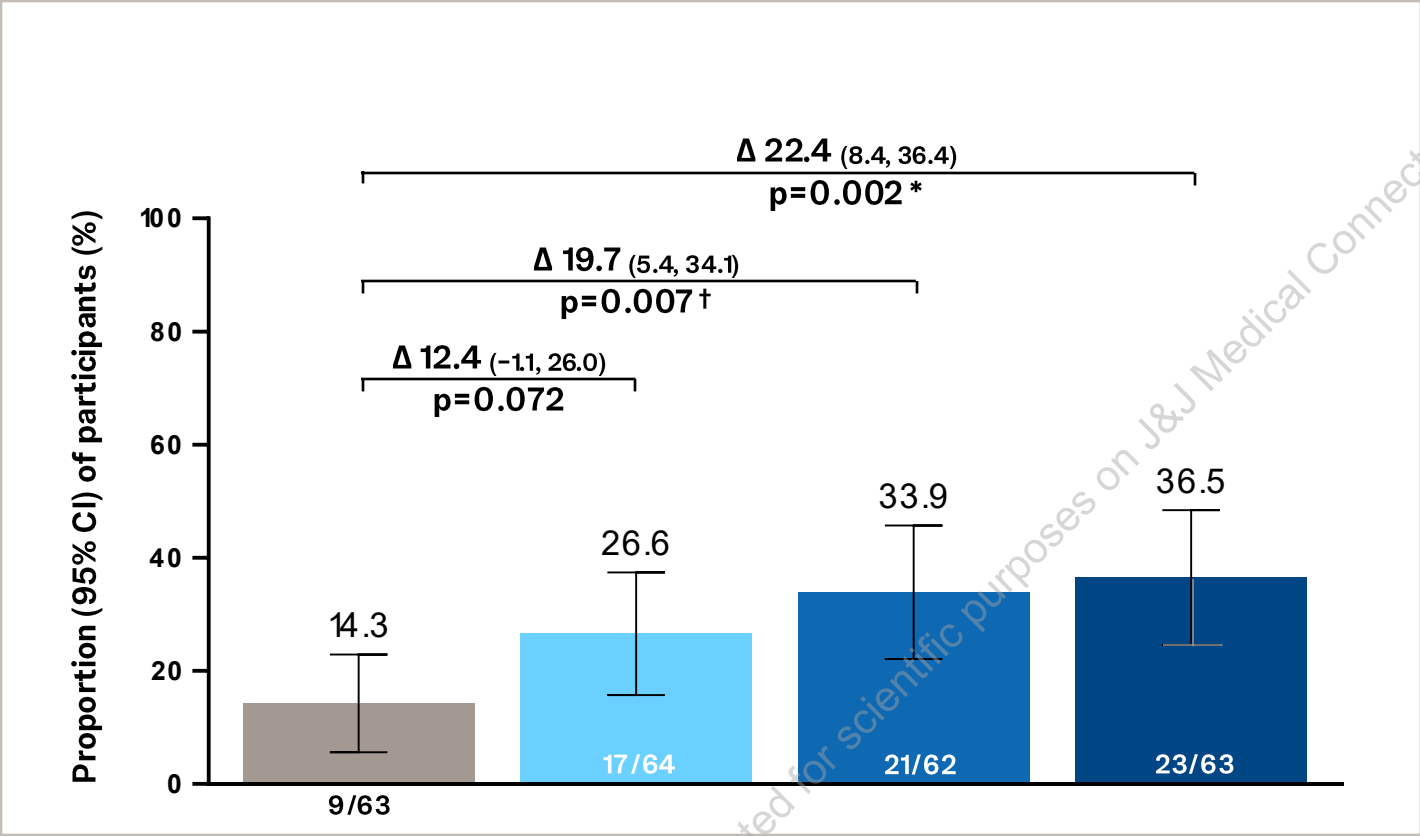
Symptomatic Remission Through Week 12



Symptomatic remission: stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopic subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Endoscopic Improvement at Week 12



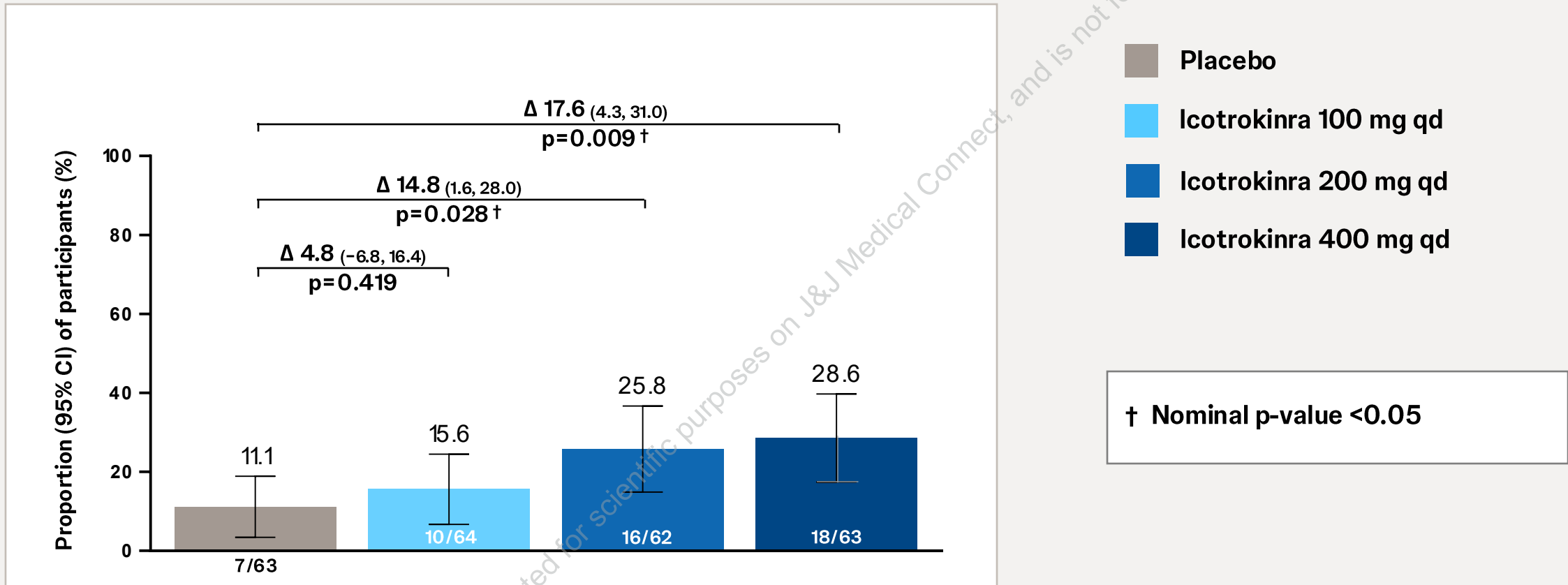
- Placebo
- Icotrokinra 100 mg qd
- Icotrokinra 200 mg qd
- Icotrokinra 400 mg qd

*** Statistically significant based on testing procedure**
† Nominal p-value <0.05

Endoscopic improvement: Mayo endoscopic subscore of 0 or 1

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/ JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopic subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Histologic–Endoscopic Mucosal Improvement (HEMI) at Week 12



Histologic-endoscopic mucosal improvement histologic remission (absence of neutrophils from the mucosa in both lamina propria and epithelium, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system) AND endoscopic improvement (MES of 0 or 1)

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/ JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopic subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Summary of Adverse Events Through Week 12

	Placebo	Icotrokinra 100 mg qd	Icotrokinra 200 mg qd	Icotrokinra 400 mg qd
Safety analysis set, N	63	64	62	63
Average duration of follow-up, weeks	11.7	12.0	12.0	11.9
Average duration of treatment, weeks	11.2	11.8	11.7	11.6
Deaths, n (%)	0	0	0	0
Participants with 1 or more, n (%)				
AEs	32 (50.8%)	32 (50.0%)	28 (45.2%)	29 (46.0%)
Serious AEs	3 (4.8%)	0	2 (3.2%)	1 (1.6%)
AEs leading to discontinuation of study agent	5 (7.9%)	0	4 (6.5%)	1 (1.6%)
Infections^a	12 (19.0%)	11 (17.2%)	16 (25.8%)	12 (19.0%)
Serious infections^a	1 (1.6%)	0	0	0
Most common AEs (frequency ≥5% in any group), n (%)				
Worsening of ulcerative colitis	5 (7.9%)	3 (4.7%)	5 (8.1%)	3 (4.8%)
Headache	1 (1.6%)	5 (7.8%)	2 (3.2%)	4 (6.3%)
Upper respiratory tract infection	1 (1.6%)	4 (6.3%)	3 (4.8%)	4 (6.3%)
Nasopharyngitis	1 (1.6%)	3 (4.7%)	0	6 (9.5%)
COVID-19	0	0	4 (6.5%)	0

a. Infections were defined as any adverse event coded to the MedDRA system organ class 'Infections and infestations'.

Conclusions



In adults with moderately to severely active ulcerative colitis, all tested doses of once-daily oral icotrokinra achieved the primary endpoint of clinical response at Week 12



At Week 12, icotrokinra 400 mg qd was superior to placebo for clinical remission, symptomatic remission, and endoscopic improvement with clinically meaningful differences observed for histologic–endoscopic mucosal improvement (HEMI)



Icotrokinra was well tolerated: the proportions of participants experiencing AEs through Week 12 were similar for placebo and all icotrokinra doses



Icotrokinra, the first-in-class targeted oral peptide that selectively blocks the IL-23 receptor, has potential to offer therapeutic benefit with a favorable safety profile in a once-daily oral treatment for ulcerative colitis

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- This work was supported by Johnson & Johnson

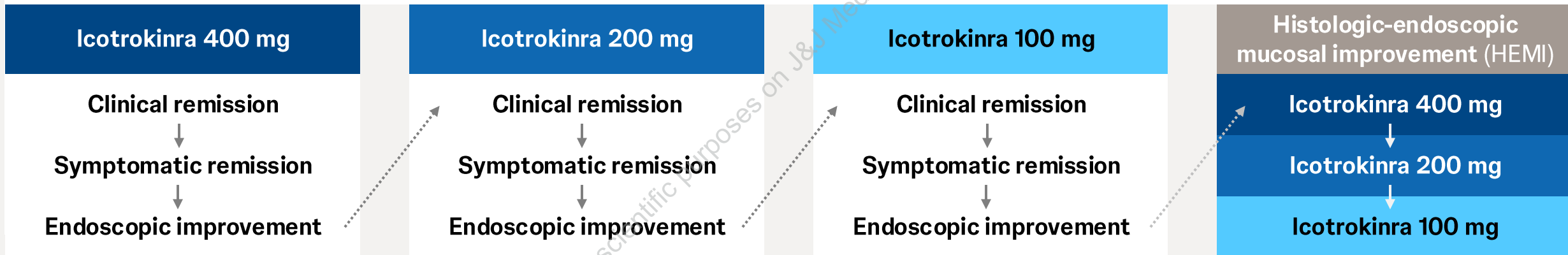
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Multiple Testing Procedure and Statistical Considerations

Primary Endpoint: Clinical response vs placebo at Week 12

- Evaluated first for **Icetrokinra 400 mg** then **Icetrokinra 200 mg** then **Icetrokinra 100 mg**

Secondary Endpoints (all vs placebo at Week 12)



- ✓ The study was powered to detect a treatment difference between icetrokinra 400 mg and placebo for the primary endpoint; it was not powered for the secondary endpoints
- ✓ Statistical testing was conducted sequentially: if a comparison was $p \geq 0.05$, all subsequent comparisons were not significant and nominal p-values are presented