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GUSELKUMAB FOR PERIANAL FISTULIZING CROHN'S DISEASE: WEEK 24 RESULTS FROM THE PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER FUZION STUDY

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SPEAKER DISCLOSURE

Laurent Peyrin-Biroulet

I disclose the following financial relationships with a commercial interest:

- CONSULTING: Abbvie, Abivax, Adacyte, Alimentiv, Alfasigma, Amgen, Apini, Banook, BMS, Celltrion, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, GSK, Hemay, Iterative Health, Janssen, Lilly, LifeMine, Medac, Mirador, Morphic, MSD, Nordic Pharma, Novartis, Oddifact, Oncodesign Precision Medicine, Onco3R, ONO Pharma, OSE Immunotherapeuthics, Palisade Bio, Par' Immune, Pfizer, Prometheus, Roche, Roivant, Samsung, Sandoz, Sanofi, Sorriso, Spyre, Takeda, Teva, ThirtyfiveBio, Tillots, Vectivbio, Vedanta, Ventyx
- STOCK AND/OR STOCK OPTIONS: Iterative Health, Oragen, Pharmanest, Thetis
- LECTURE FEES: Abbvie, Alfasigma, Amgen, Biogen, Celltrion, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Iterative Health, Janssen, Lilly, Medac, MSD, Nordic Pharma, Novartis, Pfizer, Roche, Sandoz, Takeda, Tillots

Perianal Fistulizing Crohn's Disease

Severe and **complex manifestation of CD** characterized by the development of abnormal epithelial connections between the anorectal canal and perianal skin[1,2]

PFCD affects ~**1/4th** of patients and presence at diagnosis may indicate a more severe clinical course of CD[3]

PFCD is often accompanied by[1,2,4]

- Perianal abscesses
- Pain and persistent drainage/discharge
- Fecal incontinence
- Impaired QoL

1. Lee JJ. *Clin Exp Gastroenterol.* 2025;18:291-303. **2.** Anand E. *Tech Coloproctol.* 2025;29(1):102. **3.** Lichtenstein GR. *Am J Gastroenterol.* 2025;120(6):1225-1264. **4.** Hanna LN. *Clin Gastroenterol Hepatol.* 2025;23(6):914-926. **CD**=Crohn's disease, **PFCD**=perianal fistulizing Crohn's disease, **QoL**=quality of life.

Background and Objective

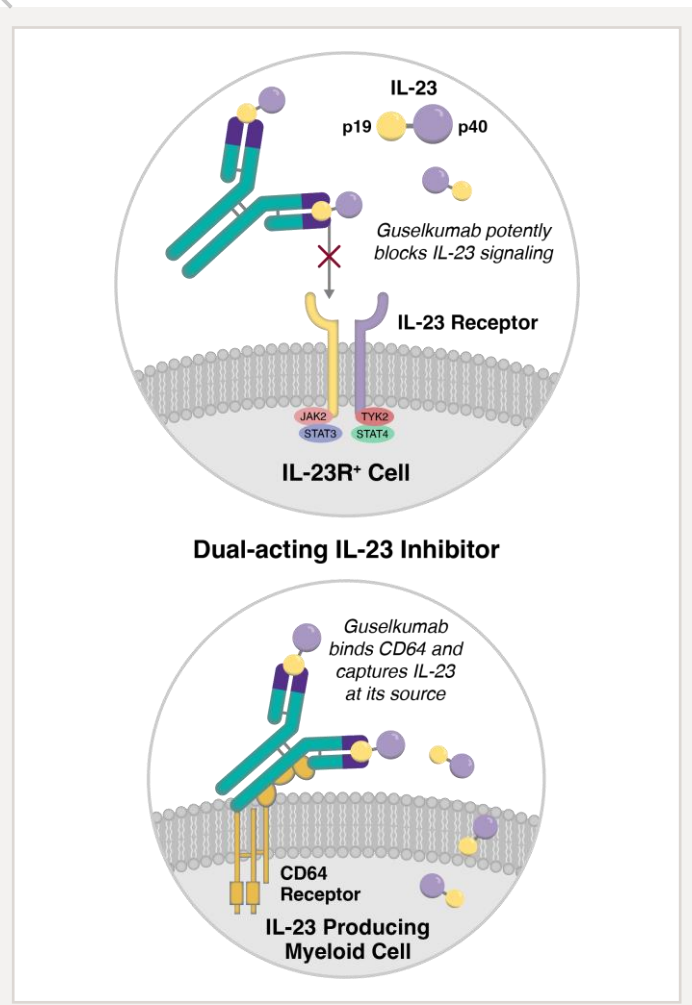
Despite combined medical-surgical management, durable fistula healing remains challenging

The last successful international, randomized, placebo-controlled trial of an advanced therapy dedicated to evaluating fistulizing Crohn's disease was the ACCENT 2 trial of infliximab, which was published in 2004[1]

Guselkumab:

- Fully human, dual-acting monoclonal antibody that selectively inhibits interleukin (IL)-23 by targeting its p19 subunit and binds to CD64, a receptor on immune cells that produces IL-23[2]
- Approved for adults with moderately-to-severely active Crohn's disease[2]

Objective: In the FUZION study (NCT05347095), a Phase 3, randomized, placebo-controlled, double-blind, international study, we evaluated the efficacy and safety of guselkumab in adults with active perianal fistulizing Crohn's disease

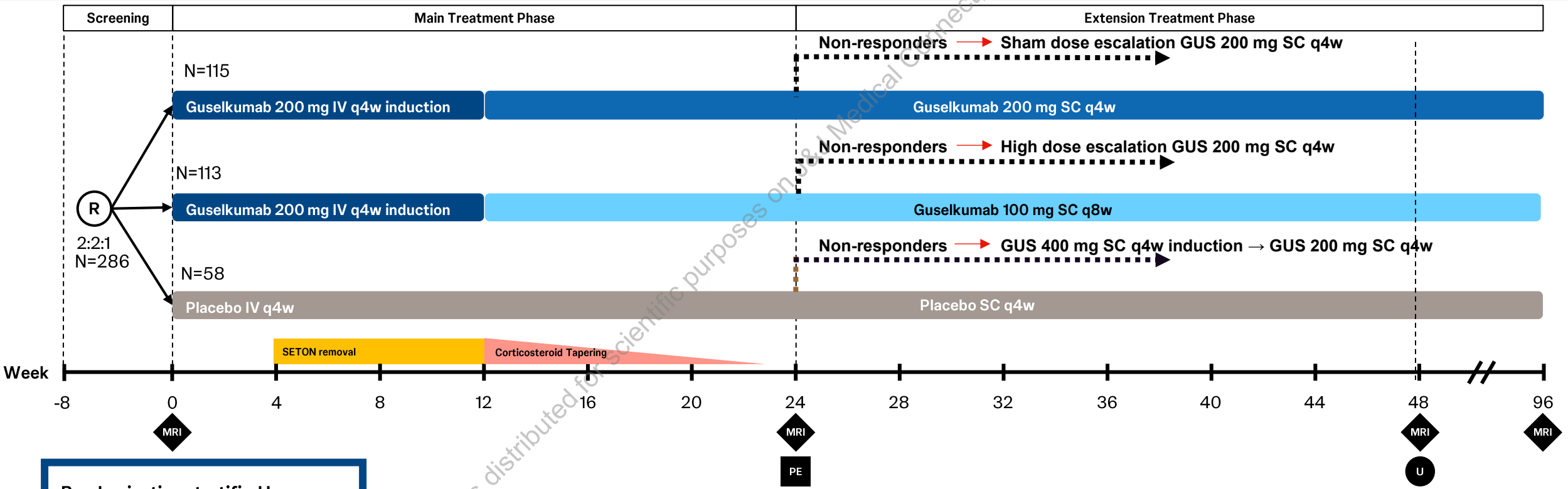


1. Sands BE. *N Engl J Med.* 2004;350:876-85. **2.** Sachen KL. *Front Immunol.* 2025;16:1532852. doi: 10.3389/fimmu.2025.1532852. **3.** Tremfya (guselkumab) [Prescribing Information. Revised 09/2025] Available from: https://www.jnjlabels.com/package-insert/product-monograph/prescribing-information/TREMFYA-pi.pdf.

Phase 3, Double-Blind, Treat-Through Study

Key Eligibility Criteria

- Adults with at least 1 active draining perianal fistula confirmed by blinded central MRI review
- Active Crohn's disease (CDAI score <350)
- Inadequate response or intolerance to oral corticosteroids, azathioprine, 6-mercaptopurine, methotrexate or up to 2 advanced therapy classes (anti-TNF, vedolizumab, JAK inhibitors) and be refractory to antibiotics (ie, ciprofloxacin, metronidazole)



Randomization stratified by:
- Proctitis (Y/N), assessed by MRI
- Prior bionaive status (Y/N)

Fistula-related surgery and the use of antibiotics were allowed, according to local practice, during screening

CDAI=Crohn's disease activity index, **IV**=intravenous, **JAK**=Janus kinase, **MRI**=Magnetic Resonance Imaging, **PE**=primary endpoint, **q4W**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **TNF**=tumor necrosis factor, **U**=study unblinding.

Endpoints through Week 24*

Primary Endpoint*

Combined fistula **remission** at week 24 (clinically and radiologically assessed)

Multiplicity-Controlled Secondary Endpoints*

- Clinically assessed fistula **remission** at week 24
- Clinically assessed fistula **response** at week 24

Key Secondary Endpoints

- Clinically assessed fistula **response** at week 12

Assessment Type	Outcome	Definition
Clinical	Clinically assessed fistula **remission**	100% closure of all treated external openings, without development of new fistulas or abscesses and without any drainage by the external openings, occurring spontaneously or after gentle finger compression
	Clinically assessed fistula **response**	≥50% reduction from baseline in number of open or draining perianal fistulas
Radiological	Absence of collections >2cm	Absence of collections >2 cm of the perianal fistulas, confirmed by a blinded central review of the MRI results

*In the statistical testing procedure, guselkumab 200 mg q4w dose then the 100 mg q8w dose were sequentially tested versus placebo for the primary endpoint then for the multiplicity-controlled secondary endpoints.

Combined fistula remission definition was previously used in Panés, J. *Lancet.* 2016: 388: 1281-90. **MRI**=Magnetic Resonance Imaging, **q4w**=every 4 weeks, **q8w**=every 8 weeks.

Demographics and Baseline Disease Characteristics

	100 mg SC q8w (N=113)	200 mg SC q4w (N=115)	Combined (N=228)	Placebo (N=58)	Total (N=286)
Age, mean (SD) (years)	36.2 (12.67)	36.0 (13.02)	36.1 (12.82)	38.0 (12.93)	36.5 (12.84)
Male, n (%)	79 (69.9%)	85 (73.9%)	164 (71.9%)	41 (70.7%)	205 (71.7%)
Crohn's disease duration (years)					
Median	5.56	6.77	6.08	7.75	6.29
IQ range	(1.90; 15.64)	(2.07; 15.93)	(1.94; 15.75)	(3.41; 17.59)	(2.07; 15.93)
CDAI Score, N	113	108	221	56	277
Mean (SD)	154.6 (97.57)	143.2 (84.60)	149.0 (91.43)	147.6 (104.26)	148.7 (93.97)
> 220	25 (22.1%)	23 (21.3%)	48 (21.7%)	10 (17.9%)	58 (20.9%)
≤ 220	88 (77.9%)	85 (78.7%)	173 (78.3%)	46 (82.1%)	219 (79.1%)
Participants with open or draining fistula, n (%)					
1 fistula	73 (64.6%)	60 (52.2%)	133 (58.3%)	33 (56.9%)	166 (58.0%)
>1 fistulas	40 (35.4%)	55 (47.8%)	95 (41.7%)	25 (43.1%)	120 (42.0%)
Previous biologic exposure, n (%)					
Bio-naive	43 (38.1%)	38 (33.0%)	81 (35.5%)	16 (27.6%)	97 (33.9%)
Bio-exposed	70 (61.9%)	77 (67.0%)	147 (64.5%)	42 (72.4%)	189 (66.1%)
Proctitis at baseline, n (%)	31 (27.4%)	37 (32.2%)	68 (29.8%)	16 (27.6%)	84 (29.4%)
Seton present at baseline, n (%)	23 (20.4%)	21 (18.3%)	44 (19.3%)	10 (17.2%)	54 (18.9%)
≥1 fistula-related surgery during screening, n (%)	31 (27.4%)	30 (26.1%)	61 (26.8%)	13 (22.4%)	74 (25.9%)
Patients with collections >2 cm at baseline, n(%)	0	4 (3.5%)	4 (1.8%)	2 (3.4%)	6 (2.1%)

CDAI=Crohn's disease activity index, **IQ**=interquartile range, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **SD**=standard deviation.

Prior and Concomitant Medications for Crohn's Disease

	100 mg SC q8w (N=113)	200 mg SC q4w (N=115)	Combined (N=228)	Placebo (N=58)	Total (N=286)
Inadequate response or intolerance, n (%)	70 (61.9%)	77 (67.0%)	147 (64.5%)	42 (72.4%)	189 (66.1%)
Infliximab	52 (46.0%)	58 (50.4%)	110 (48.2%)	32 (55.2%)	142 (49.7%)
Adalimumab	38 (33.6%)	42 (36.5%)	80 (35.1%)	23 (39.7%)	103 (36.0%)
Certolizumab	1 (0.9%)	2 (1.7%)	3 (1.3%)	1 (1.7%)	4 (1.4%)
Vedolizumab	8 (7.1%)	6 (5.2%)	14 (6.1%)	3 (5.2%)	17 (5.9%)
Ustekinumab*	4 (3.5%)	3 (2.6%)	7 (3.1%)	5 (8.6%)	12 (4.2%)
Only 1 anti-TNF agent	43 (38.1%)	51 (44.3%)	94 (41.2%)	27 (46.6%)	121 (42.3%)
>1 anti-TNF agent	24 (21.2%)	25 (21.7%)	49 (21.5%)	14 (24.1%)	63 (22.0%)
Only one mechanism of action	62 (54.9%)	69 (60.0%)	131 (57.5%)	35 (60.3%)	166 (58.0%)
Concomitant medications for CD at baseline, n (%)					
5-ASA	27 (23.9%)	27 (23.5%)	54 (23.7%)	19 (32.8%)	73 (25.5%)
Corticosteroids	10 (8.8%)	9 (7.8%)	19 (8.3%)	3 (5.2%)	22 (7.7%)
Immunosuppressants (AZA, 6-MP, MTX)	34 (30.1%)	35 (30.4%)	69 (30.3%)	16 (27.6%)	85 (29.7%)

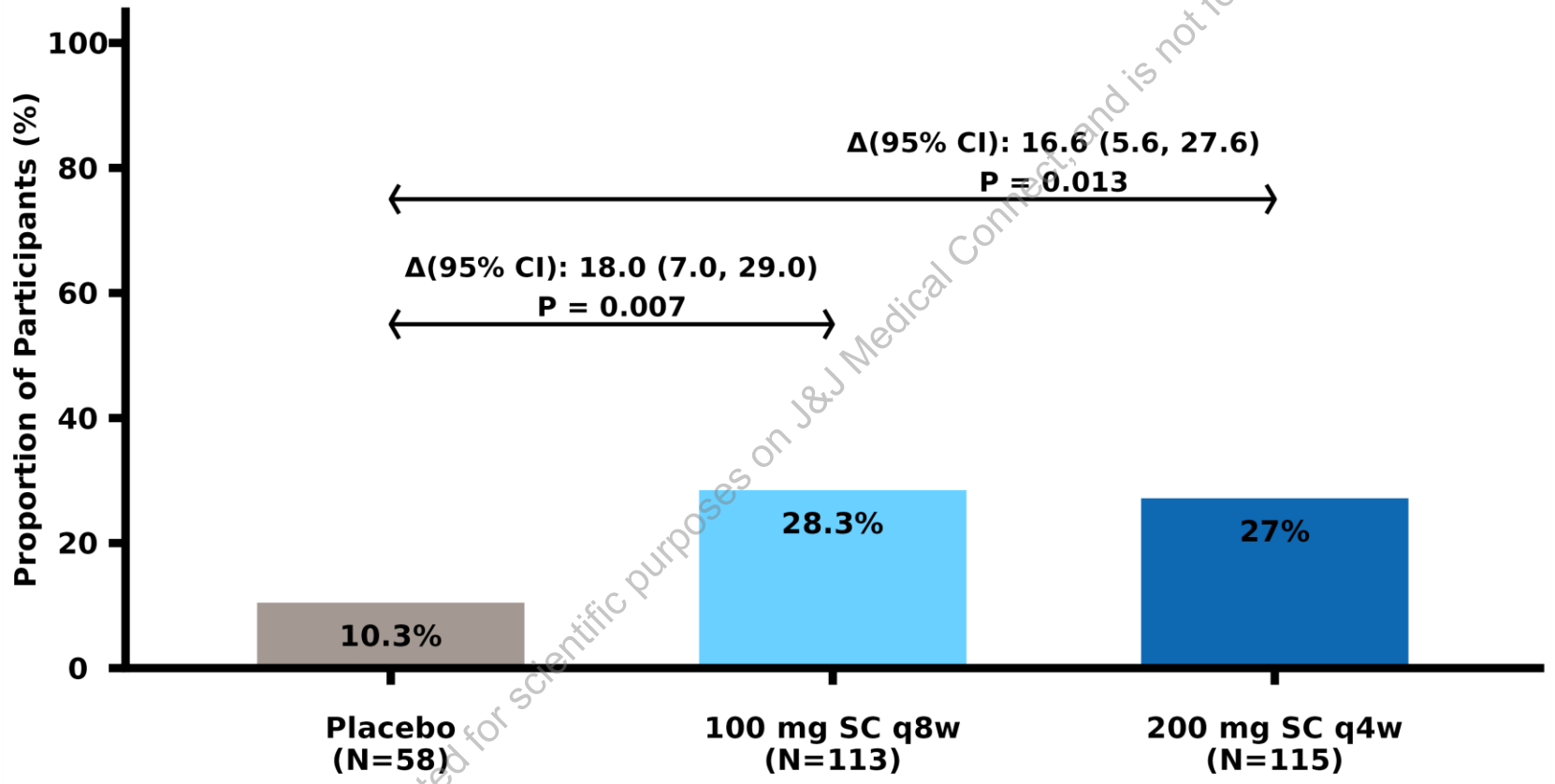
Participants with prior exposure to IL-12/23 or IL-23 agents were ineligible for study entry. *Participants who were exposed to ustekinumab at its approved labeled dosage AND met the required washout criterion (16 weeks) AND had not demonstrated inadequate response or intolerance to ustekinumab AND received one IV induction dose of ~6 mg/kg and one SC maintenance dose of 90 mg.
ASA=aminosalicylates, **AZA**=azathioprine, **CD**=Crohn's disease, **MP**=mercaptopurine, **MTX**=methotrexate, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **TNF**=tumor necrosis factor.

Discontinuation of Study Agent Before Week 24

	100 mg SC q8w (N=113)	200 mg SC q4w (N=115)	Combined (N=228)	Placebo (N=58)	Total (N=286)
Completed 24 weeks of treatment, n (%)	100 (88.5%)	111 (96.5%)	211 (92.5%)	50 (86.2%)	261 (91.3%)
Discontinued study treatment, n (%)	13 (11.5%)	4 (3.5%)	17 (7.5%)	8 (13.8%)	25 (8.7%)
Reason for discontinuing study treatment, n (%)					
Discontinued due to AE	9 (8.0%)	3 (2.6%)	12 (5.3%)	4 (6.9%)	16 (5.6%)
Adverse event - Other	4 (3.5%)	3 (2.6%)	7 (3.1%)	0	7 (2.4%)
Adverse event - Worsening of Crohn's disease	5 (4.4%)	0	5 (2.2%)	4 (6.9%)	9 (3.1%)
Death	0	0	0	0	0
Lack of efficacy	0	0	0	1 (1.7%)	1 (0.3%)
Lost to follow-up	1 (0.9%)	0	1 (0.4%)	0	1 (0.3%)
Physician Decision	1 (0.9%)	0	1 (0.4%)	0	1 (0.3%)
Protocol deviation	0	0	0	0	0
Pregnancy	0	0	0	0	0
Subject refused further study treatment	0	0	0	1 (1.7%)	1 (0.3%)
Withdrawal of consent	2 (1.8%)	0	2 (0.9%)	0	2 (0.7%)
Prohibited Crohn's Disease related surgery	0	0	0	0	0
Other	0	1 (0.9%)	1 (0.4%)	2 (3.4%)	3 (1.0%)

AE=adverse event, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous.

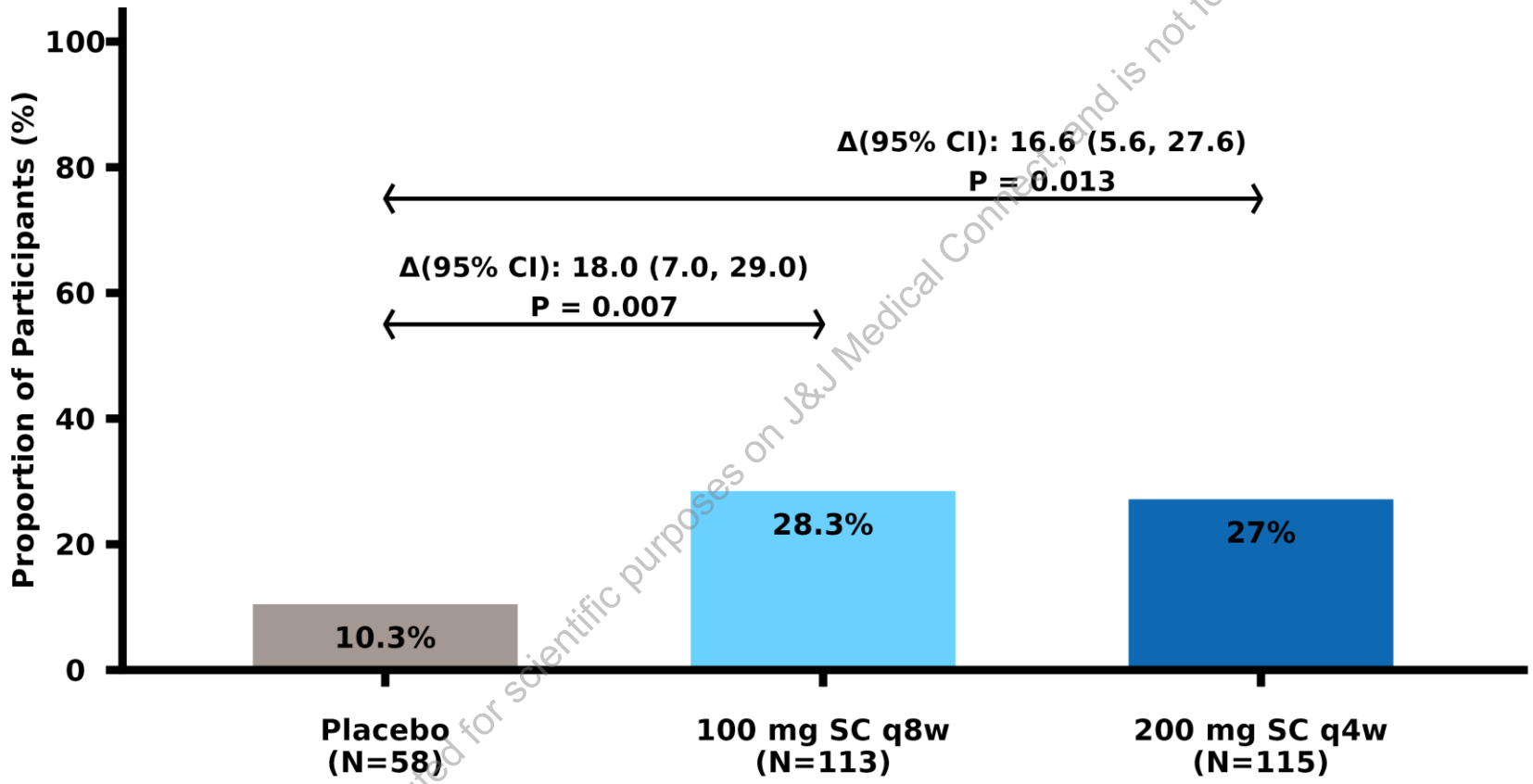
Combined Fistula Remission at Week 24
Primary Endpoint



Combined Fistula Remission: 100% closure of all treated external openings, without development of new fistulas or abscesses and without any drainage by the external openings, occurring spontaneously or after gentle finger compression AND absence of collections >2 cm of the perianal fistulas, confirmed by a blinded central review of the MRI results

Missing Data Imputation: After applying the ICE strategy, missing data were imputed as not having achieved a combined fistula remission at week 24. The adjusted risk difference and CI were based on Wald statistics using Mantel-Haenszel stratum weights stratified by baseline proctitis (yes, no) and baseline bio-naïve status (yes, no). The p-values are based on the CMH test, stratified by baseline proctitis (yes, no) and baseline bio-naïve status (yes, no). **CI**=confidence interval, **CMH**=Cochran-Mantel-Haenszel, **ICE**=intercurrent event, **MRI**=magnetic resonance imaging, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous.

Clinically Assessed Fistula Remission at Week 24
Multiplicity-Controlled Secondary Endpoint



Clinically Assessed Fistula Remission: 100% closure of all treated external openings, without development of new fistulas or abscesses and without any drainage by the external openings, occurring spontaneously or after gentle finger compression

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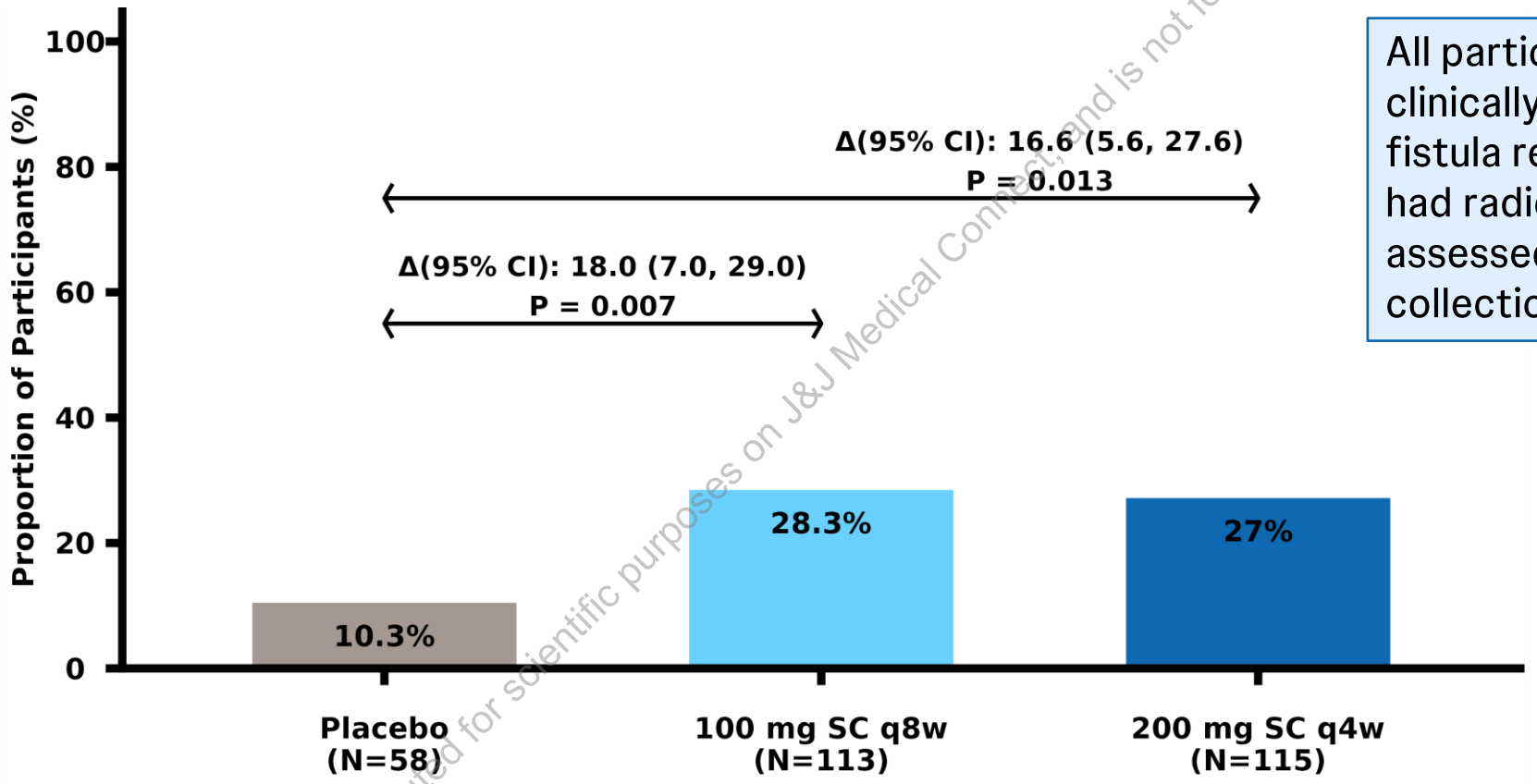
Clinically Assessed Fistula Remission at Week 24
Multiplicity-Controlled Secondary Endpoint

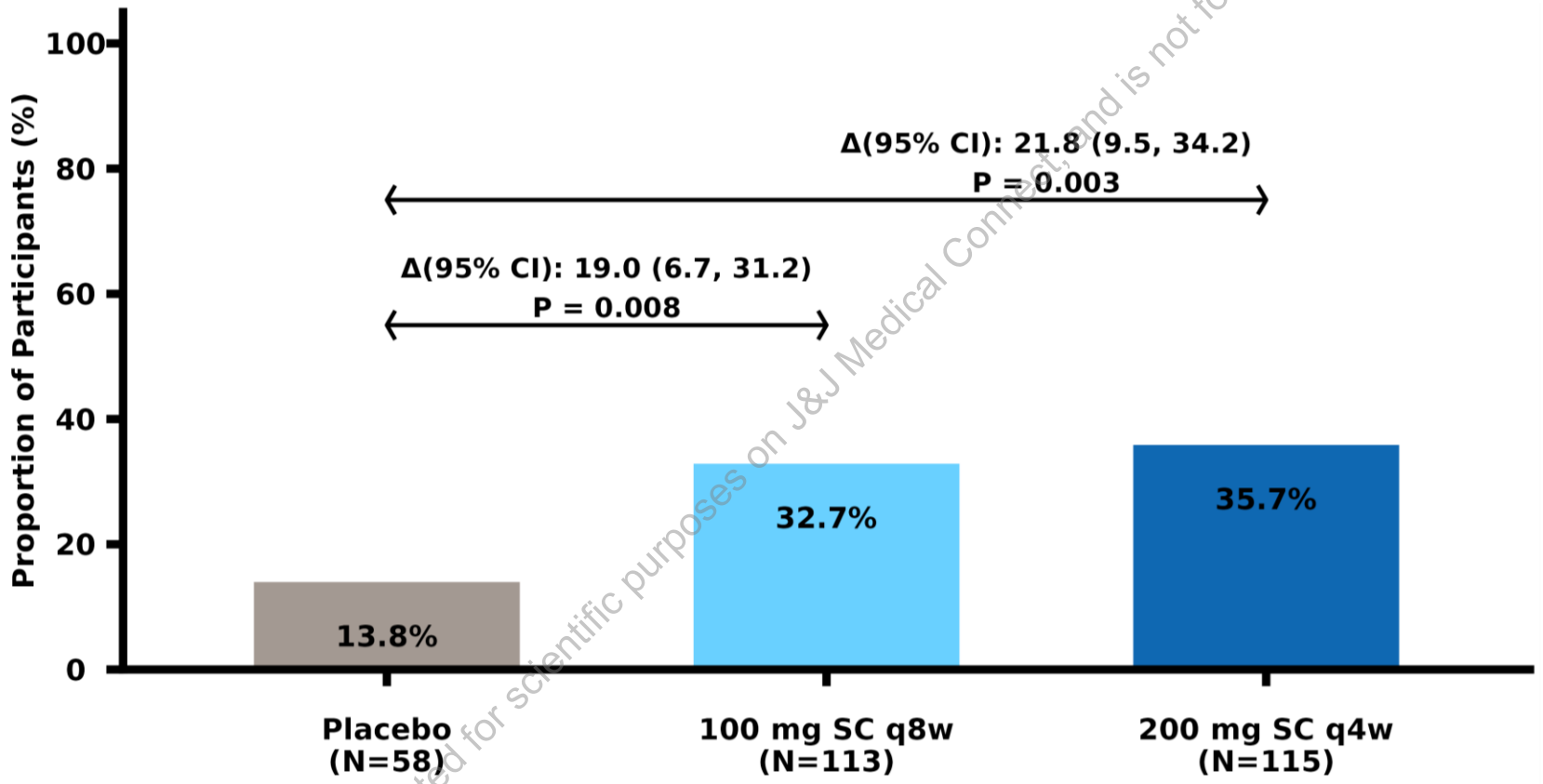


All participants who had clinically assessed fistula remission also had radiologically assessed absence of collections >2cm

Clinically Assessed Fistula Remission: 100% closure of all treated external openings, without development of new fistulas or abscesses and without any drainage by the external openings, occurring spontaneously or after gentle finger compression

Missing Data Imputation: After applying the ICE strategy, missing data were imputed as not having achieved a combined fistula remission at week 24. The adjusted risk difference and CI were based on Wald statistics using Mantel-Haenszel stratum weights stratified by baseline proctitis (yes, no) and baseline bio-naïve status (yes, no). The p-values are based on the CMH test, stratified by baseline proctitis (yes, no) and baseline bio-naïve status (yes, no). **CI**=confidence interval, **CMH**=Cochran-Mantel-Haenszel, **ICE**=intercurrent event, **MRI**=magnetic resonance imaging, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous.

Clinically Assessed Fistula Response at Week 24
Multiplicity-Controlled Secondary Endpoint

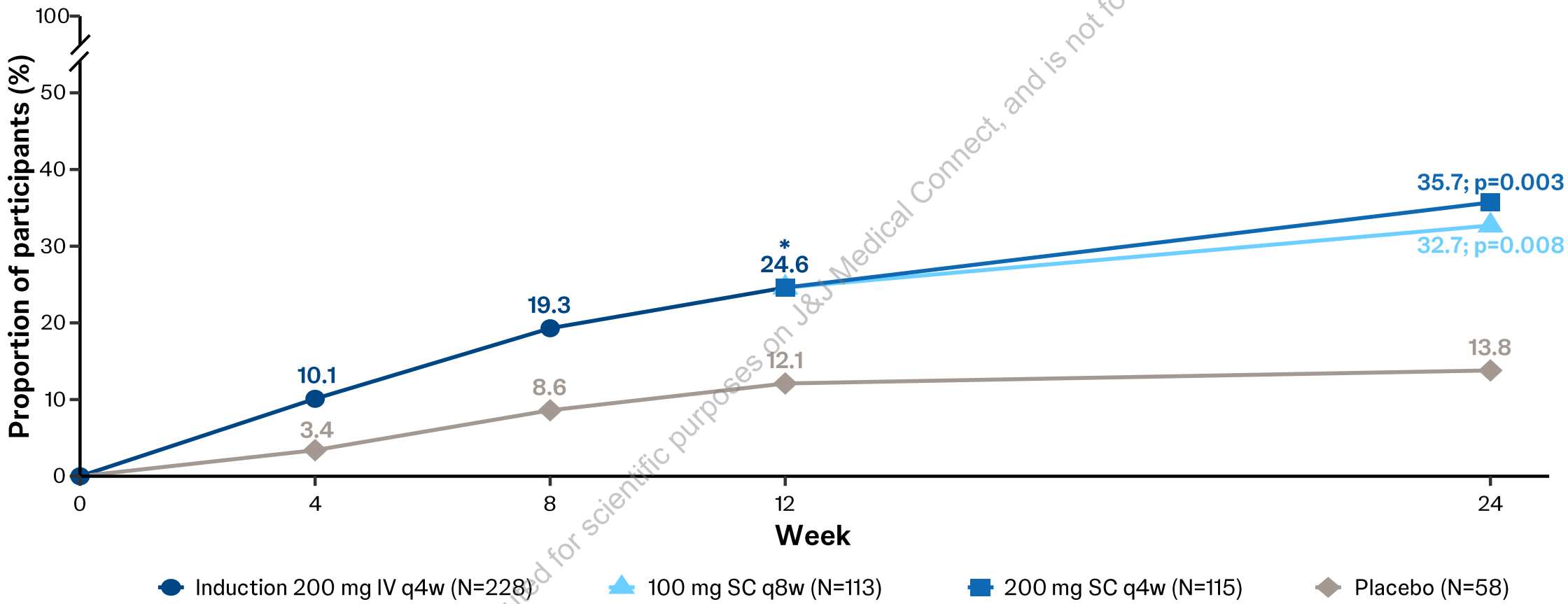


Clinically Assessed Fistula Response: ≥50% reduction from baseline in number of open or draining perianal fistulas

Missing Data Imputation: After applying the ICE strategy, missing data were imputed as not having achieved a combined fistula remission at week 24. The adjusted risk difference and CI were based on Wald statistics using Mantel-Haenszel stratum weights stratified by baseline proctitis (yes, no) and baseline bio-naïve status (yes, no). The p-values are based on the CMH test, stratified by baseline proctitis (yes, no) and baseline bio-naïve status (yes, no). **CI**=confidence interval, **CMH**=Cochran-Mantel-Haenszel, **ICE**=intercurrent event, **MRI**=magnetic resonance imaging, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous.

Clinically Assessed Fistula Response through Week 24

Guselkumab showed meaningful difference versus placebo during induction



Clinically Assessed Fistula Response: ≥50% reduction from baseline in number of open or draining perianal fistulas

*Nominal p=0.041

Missing Data Imputation: After applying the ICE strategy, missing data were imputed as not having achieved a combined fistula remission at Week 24. The adjusted risk difference and CI were based on Wald statistics using Mantel-Haenszel stratum weights stratified by baseline proctitis (yes, no) and baseline bio-naïve status (yes, no). The p-values are based on the CMH test, stratified by baseline proctitis (yes, no) and baseline bio-naïve status (yes, no). **CI**=confidence interval, **CMH**=Cochran-Mantel-Haenszel, **ICE**=intercurrent event, **IV**=intravenous, **MRI**=magnetic resonance imaging, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous.

Adverse Events through Week 24

	100 mg SC q8w (N=113)	200 mg SC q4w (N=115)	Combined (N=228)	Placebo (N=58)
Mean duration of follow-up (weeks)	24.0	24.0	24.0	23.8
Mean exposure (number of study agent administrations)	5.7	5.8	5.8	5.6
Subjects with ≥1 adverse event	76 (67.3%)	80 (69.6%)	156 (68.4%)	48 (82.8%)
Subjects with ≥1 serious adverse event	12 (10.6%)	7 (6.1%)	19 (8.3%)	8 (13.8%)
Subjects with ≥1 adverse event leading to discontinuation of study agent	8 (7.1%)	3 (2.6%)	11 (4.8%)	5 (8.6%)
Subjects with ≥1 infection	45 (39.8%)	31 (27.0%)	76 (33.3%)	27 (46.6%)
Subjects with ≥1 serious infection	8 (7.1%)	2 (1.7%)	10 (4.4%)	2 (3.4%)

- No opportunistic infection, anaphylactic reactions or serum sickness reactions, MACE, clinically important hepatic disorders and VTE or deaths were reported
- **1 malignancy** a B-cell lymphoma was reported through Week 24 **(not related to study drug as assessed by investigator)**
- Injection-site reactions were **mild** and did not lead to discontinuation

Infections are based on MedDRA system organ class "Infections and Infestations". Subjects are counted only once for any given event under specific column, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 28.0. **MACE**=major adverse cardiovascular event, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **VTE**=venous thrombo-embolic event.

Conclusions

- FUZION is the first successful international phase 3 study that assessed a combined clinical and MRI primary endpoint and the first in more than two decades that showed efficacy of an advanced therapy in perianal fistulizing Crohn's disease

- Guselkumab was efficacious through Week 24 in a bio-naïve and bio-exposed population of patients with perianal fistulizing Crohn's disease
  - ✓ Guselkumab showed clinically meaningful difference versus placebo during induction
  - ✓ Both guselkumab maintenance doses showed statistically significant and clinically meaningful benefit compared with placebo

- The guselkumab benefit-risk profile was favorable, with no new safety signals identified

Acknowledgements

- The authors thank the participants, investigators, and study personnel who made FUZION possible

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