

Efficacy and Safety of Guselkumab in Perianal Fistulizing Crohn's Disease: Week 48 Results From the Phase 3, Randomized, Double-Blind, Placebo-Controlled FUZION Trial

[Ailsa Hart](#),¹ Axel Dignass,² Vipul Jairath,³ Tadakazu Hisamatsu,⁴ Bruce E. Sands,⁵ Antonino Spinelli,^{6,7} Susan J. Connor,⁸ André D'Hoore,⁹ Walter Reinisch,¹⁰ Silvio Danese,¹¹ David A. Schwartz,¹² Julian Panés,¹³ Bram Verstockt,¹⁴ Anton Stift,¹⁵ Maciej Nazar,¹⁶ Jacqueline van Denderen,¹⁷ Takehiko Sakamoto,¹⁸ Koji Masuda,¹⁸ Stephen Xu,¹⁹ Ivana Bravatà,²⁰ Geert D'Haens,²¹ and Laurent Peyrin-Biroulet²² on behalf of the FUZION Study Group

¹St Mark's, the National Bowel Hospital, London North-West University Healthcare NHS Trust, London, United Kingdom;

²Department of Medicine I, Agaplesion Markus Hospital, Goethe University, Frankfurt, Germany; ³Department of Medicine, Schulich School of Medicine & Dentistry I, Western University, London, ON, Canada; ⁴Kyorin University School of Medicine, Tokyo, Japan;

⁵Dr. Henry D Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ⁶Department of Biomedical Sciences, Humanitas University, Pieve Emanuele - Milan, Italy; ⁷IRCCS Humanitas Research Hospital, Rozzano - Milan, Italy; ⁸Department of Gastroenterology, Liverpool Hospital, Liverpool, New South Wales and South West Sydney Clinical

Campuses, UNSW Medicine & Health, UNSW Sydney, Sydney, Australia; ⁹Department of Abdominal Surgery, University Hospitals Leuven, KU Leuven, Leuven, Belgium; ¹⁰Clinical Department for Gastroenterology and Hepatology, Internal Medicine Clinic III, Medical University of Vienna, Vienna, Austria; ¹¹IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milano, Italy; ¹²Inflammatory Bowel Disease Center, Vanderbilt University Medical Center, Nashville, TN, United States; ¹³Hospital Clínic de Barcelona, IDIBAPS, CIBERhd, Barcelona, Spain; ¹⁴Department of Gastroenterology and Hepatology, University Hospitals Leuven and Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium; ¹⁵Department of General Surgery, Division of Visceral Surgery, Medical University Vienna, Vienna, Austria; ¹⁶Johnson & Johnson, Warsaw, Poland; ¹⁷Johnson & Johnson, Breda, the Netherlands; ¹⁸Johnson & Johnson, Tokyo, Japan; ¹⁹Johnson & Johnson, Spring House, PA, United States; ²⁰Johnson & Johnson, Milan, Italy; ²¹Department of Gastroenterology, Amsterdam University Medical Centers, Amsterdam, The Netherlands;

²²Northwestern Medicine Digestive Health Institute, Chicago, IL, United States.



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Disclosure of Conflicts of Interest

I, Ailsa Hart, declare the following activities: lecturer and/or advisory board member for AbbVie, Bristol Myers Squibb, Celltrion, Eli Lilly, Falk, Galapagos, GlaxoSmithKline, Johnson & Johnson, MSD, Pfizer, Roche, Sanofi, Takeda, and Teva.

Background and Objective

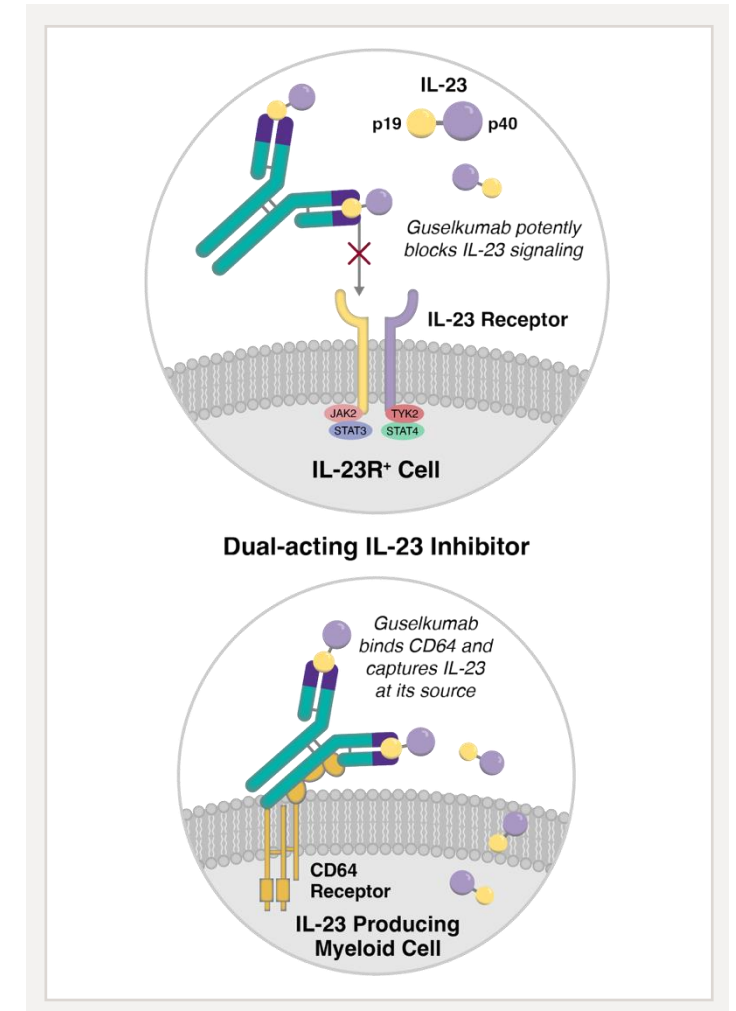
Perianal fistulizing Crohn's disease is a difficult-to-treat phenotype of Crohn's disease that impairs patients' quality of life¹

Guselkumab:

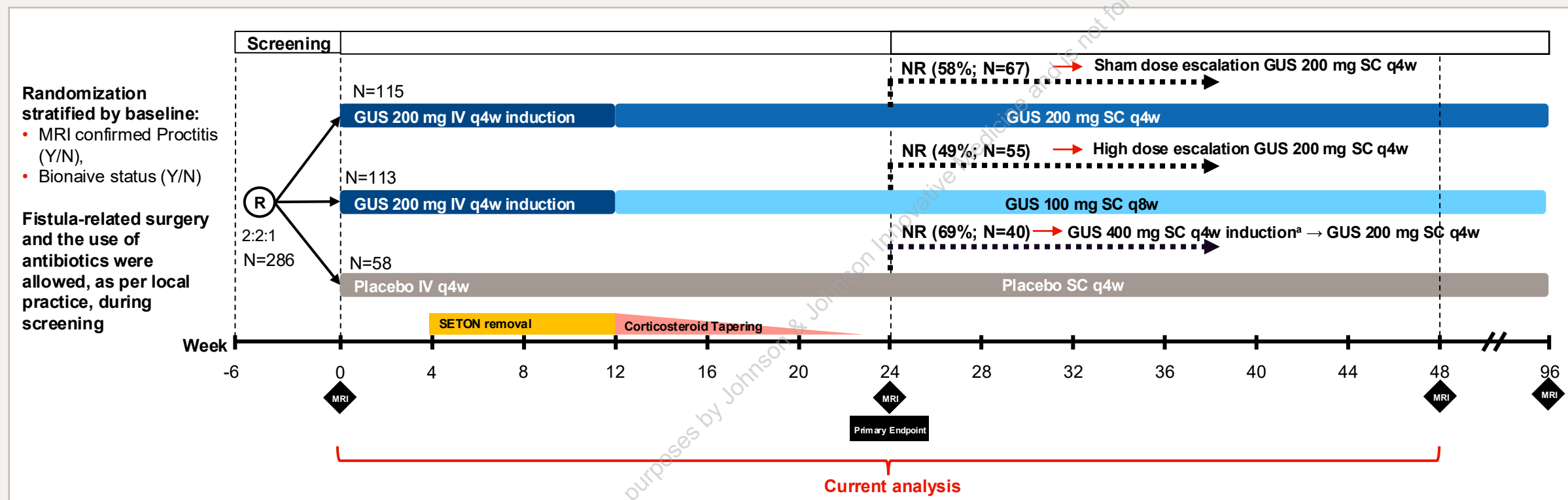
- Fully human, dual-acting monoclonal antibody that selectively inhibits interleukin (IL)-23 by targeting its p19 subunit and binds to CD64, a receptor on immune cells that produce IL-23²
- Approved for adults with moderately-to-severely active Crohn's disease³

In the Phase 3, randomized, double-blind, placebo-controlled FUZION study, guselkumab showed significant benefit versus placebo at Week 24 in patients with perianal fistulizing Crohn's disease, with no new safety signals⁴

Here we present the efficacy and safety of guselkumab through Week 48 from in the FUZION study



FUZION – Treat-through, Double-Blind Study Design



Key inclusion criteria:

- ≥18 years of age
- ≥1 active draining perianal fistula confirmed by blinded central MRI
- CDAI score <350
- Inadequate response to oral corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), antibiotics, or ≤2 advanced-therapy classes (anti-TNF, vedolizumab, JAK inhibitors, excluding prior anti-IL-12/IL-23 inhibitors^b)

Non-responders (NR; 57%):

- NR defined as <50% reduction from baseline in the number of open or draining fistulas at Week 24
- NRs across all treatment arms received one blinded dose escalation adjustment
- Responders continued with the same treatment and dose regimen through Week 48

^aIncluded 3 doses Q4W from W24 to W32. ^bParticipants 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. **CDAI**=Crohn's disease activity index, **GUS**=guselkumab, **IL**=interleukin, **IV**=intravenous, **JAK**=janus kinase, **MRI**=magnetic resonance imaging, **PE**=primary endpoint, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **R**=randomization, **SC**=subcutaneous, **TNF**=tumor necrosis factor.

Endpoints

Primary Endpoint*

Week 24: Combined fistula **remission**^a
(clinically and radiologically assessed)

Multiplicity-Controlled Secondary Endpoints*

- Week 24:
- Clinically assessed fistula **remission**
 - Clinically assessed fistula **response**

Other Secondary Endpoints

- Week 12: clinically assessed fistula **response**
- Week 48:
- Combined fistula **remission**
 - Clinically assessed fistula **remission**
 - Clinically assessed fistula **response**

Assessment Type	Outcome	Definition
Clinical	Clinically assessed fistula remission	100% closure of all 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

^aIn 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.

^aCombined 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

Baseline Characteristics	GUS 100 mg SC q8w (N=113)	GUS 200 mg SC q4w (N=115)	GUS Combined (N=228)	Placebo (N=58)
Age, yrs	36.2 (12.7)	36.0 (13.0)	36.1 (12.8)	38.0 (12.9)
Male, n (%)	79 (70%)	85 (74%)	164 (72%)	41 (71%)
Crohn's disease duration, median (IQ), yrs	5.6 (1.9; 15.6)	6.8 (2.1; 15.9)	6.1 (1.9; 15.8)	7.8 (3.4; 17.6)
CDAI score	154.6 (97.6)	143.2 (84.6) ^a	149.0 (91.4) ^b	147.6 (104.3) ^c
> 220, n (%)	25 (22%)	23 (21%)	48 (22%)	10 (18%)
≤ 220, n (%)	88 (78%)	85 (79%)	173 (78%)	46 (82%)
Participants with open or draining fistula, n (%)				
1 fistula	73 (65%)	60 (52%)	133 (58%)	33 (57%)
≥2 fistulas	40 (35%)	55 (48%)	95 (42%)	25 (43%)
Participants with complex fistula ^d , n (%)	52 (46%)	64 (56%)	116 (51%)	30 (52%)
Previous biologic exposure, n (%)				
Bio-naive	43 (38%)	38 (33%)	81 (36%)	16 (28%)
Bio-exposed	70 (62%)	77 (67%)	147 (64%)	42 (72%)
Proctitis, n (%)	31 (27%)	37 (32%)	68 (30%)	16 (28%)
Seton present, n (%)	23 (20%)	21 (18%)	44 (19%)	10 (17%)
Fistula-related surgery during screening, n (%)	17 (15%)	18 (16%)	35 (15%)	7 (12%)
Patients with collections >2 cm, n (%)	0	4 (3%)	4 (2%)	2 (3%)

Data shown are mean (SD) unless otherwise noted. ^aN=108, ^bN=221. ^cN=56. ^dFistula complexity was determined by MRI using MAGNIFI-CD "number of fistula tracts" (single/unbranched or complex). CDAI=Crohn's disease activity index, GUS=guselkumab, IQ=interquartile range, q4w=every 4 weeks, q8w=every 8 weeks, SC=subcutaneous, SD=standard deviation.

Prior and Concomitant Medications for Crohn's Disease

	GUS 100 mg SC q8w (N=113)	GUS 200 mg SC q4w (N=115)	GUS Combined (N=228)	Placebo (N=58)
Prior exposure to Crohn's disease medication, n (%)				
Infliximab	70 (62%)	77 (67%)	147 (64%)	42 (72%)
Adalimumab	52 (46%)	58 (50%)	110 (48%)	32 (55%)
Certolizumab	38 (34%)	42 (37%)	80 (35%)	23 (40%)
Vedolizumab	1 (1%)	2 (2%)	3 (1%)	1 (2%)
Ustekinumab ^a	8 (7%)	6 (5%)	14 (6%)	3 (5%)
Only 1 anti-TNF agent	4 (4%)	3 (3%)	7 (3%)	5 (9%)
≥2 anti-TNF agents	43 (38%)	51 (44%)	94 (41%)	27 (47%)
Only 1 mechanism of action	24 (21%)	25 (22%)	49 (21%)	14 (24%)
Concomitant Crohn's disease medications, n (%)				
5-ASA	62 (55%)	69 (60%)	131 (57%)	35 (60%)
Corticosteroids	27 (24%)	27 (23%)	54 (24%)	19 (33%)
Immunosuppressants (AZA, 6-MP, MTX)	10 (9%)	9 (8%)	19 (8%)	3 (5%)
	34 (30%)	35 (30%)	69 (30%)	16 (28%)

^aParticipants 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, **GUS**=guselkumab, **MP**=mercaptopurine, **MTX**=methotrexate, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **TNF**=tumor necrosis factor.

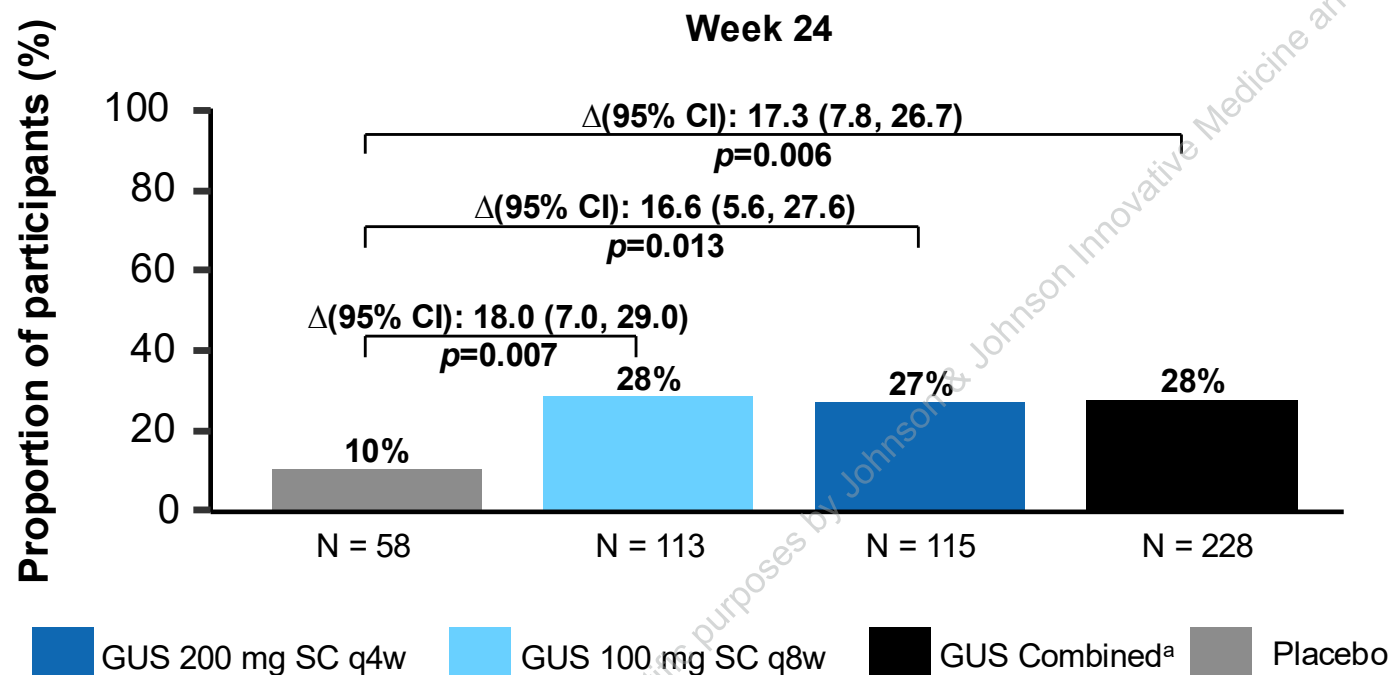
Discontinuation of Study Agent Before Week 48

	GUS 100 mg SC q8w (N=113) ^a	GUS 200 mg SC q4w (N=115) ^a	GUS Combined (N=228) ^a	Placebo (N=58) ^a
Completed 48 weeks of treatment, n (%)	97 (86%)	109 (95%)	206 (90%)	49 (84%)
Discontinued study treatment, n (%)	16 (14%)	6 (5%)	22 (10%)	9 (16%)
Reason for discontinuing study treatment, n (%)				
Discontinued due to AE	10 (9%)	5 (4%)	15 (7%)	5 (9%)
Adverse event - Other	5 (4%)	4 (3%)	9 (4%)	1 (2%)
Adverse event - Worsening of Crohn's disease	5 (4%)	1 (1%)	6 (3%)	4 (7%)
Death	0	0	0	0
Lack of efficacy	1 (1%)	0	1 (<1%)	1 (2%)
Lost to follow-up	1 (1%)	0	1 (<1%)	0
Physician Decision	1 (1%)	0	1 (<1%)	0
Protocol deviation	0	0	0	0
Pregnancy	0	0	0	0
Subject refused further study treatment	0	0	0	1 (2%)
Withdrawal of consent	3 (3%)	0	3 (1%)	0
Prohibited Crohn's Disease related surgery	0	0	0	0
Other	0	1 (1%)	1 (<1%)	2 (3%)

^aExcludes data from Week 24 to Week 48 of participants who were dose adjusted to GUS 200 mg q4w at Week 24. **AE**=adverse events, **GUS**=guselkumab, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous.

Combined Fistula Remission Through Week 24

Primary endpoint

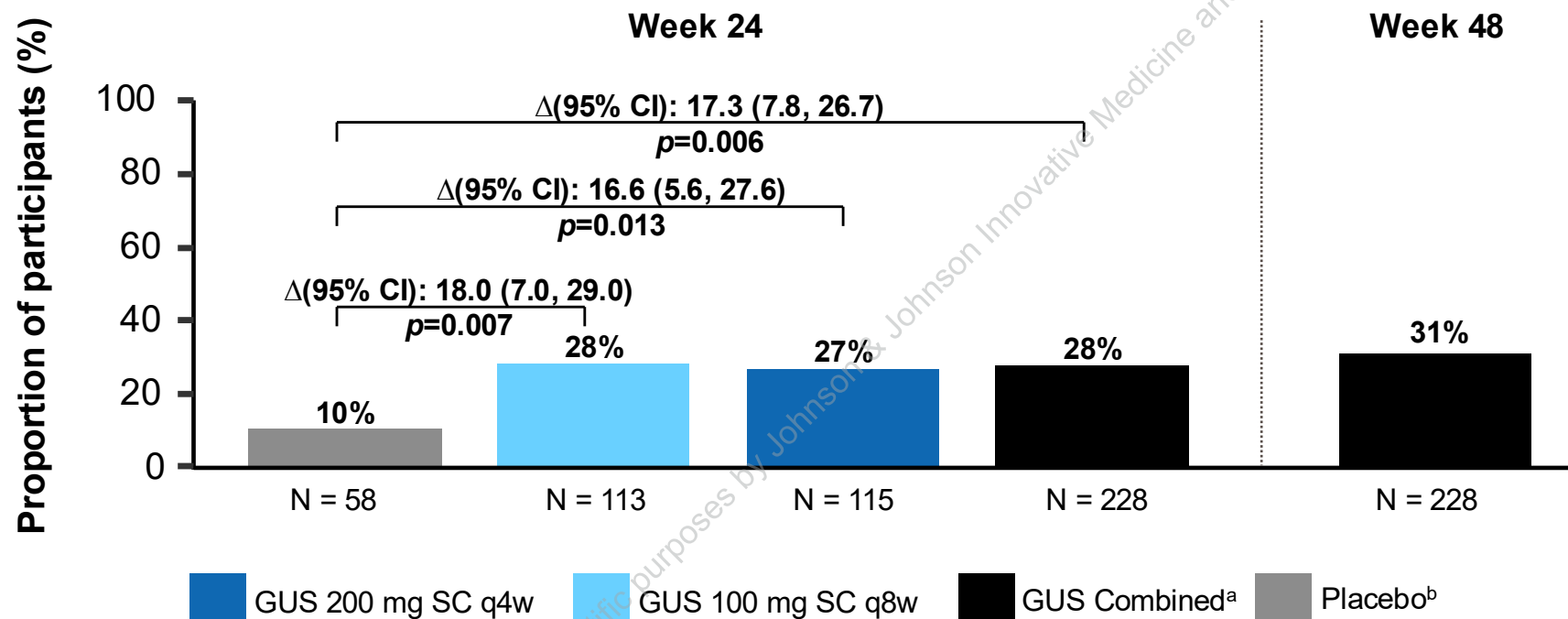


p-values are multiplicity-controlled, except for GUS combined (nominal).

Combined Fistula Remission: 100% closure of all 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

Combined Fistula Remission Through Week 48

Primary and secondary endpoints



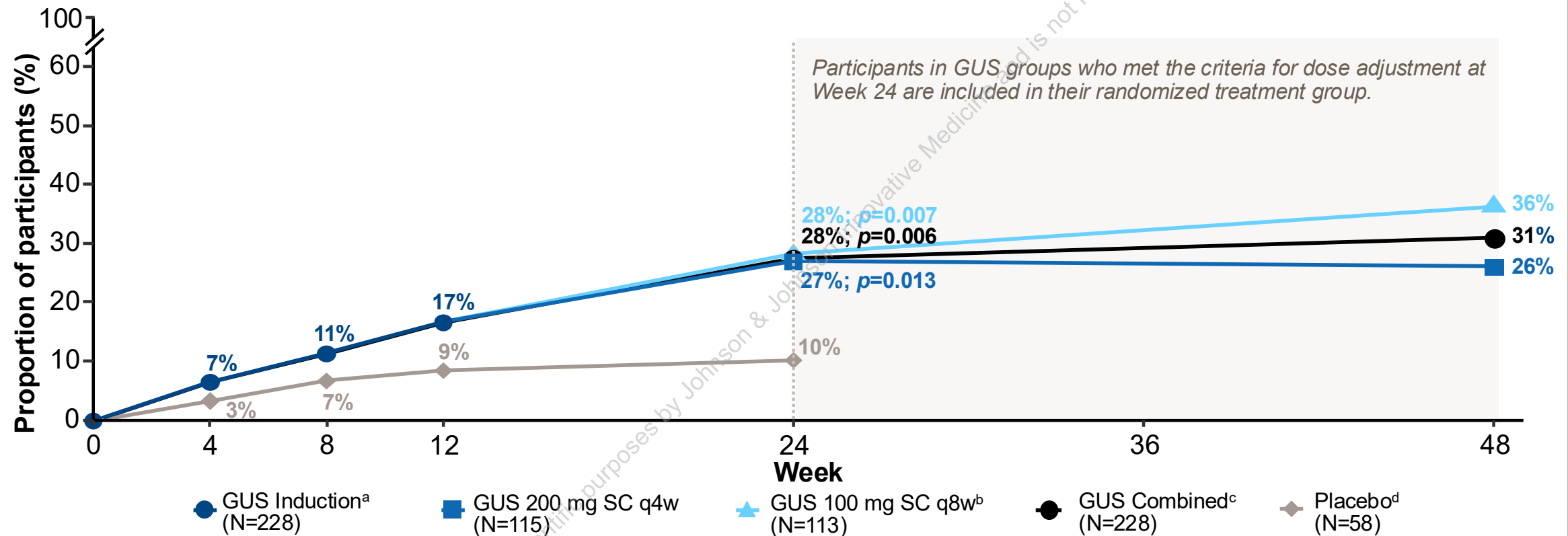
p-values are multiplicity-controlled, except for GUS combined (nominal).

Combined Fistula Remission: 100% closure of all 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

After applying the intercurrent event strategy in the statistical analysis, missing data were imputed as not having achieved binary endpoints. ^aGUS combined included both maintenance doses from Week 12 through Week 24 or Week 48, as applicable. ^bNR placebo participants received GUS after Week 24, thus no more placebo arm after Week 24. **GUS**=guselkumab, **IV**=intravenous, **NR**=non-responders, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **R**=responders, **SC**=subcutaneous.

Clinically Assessed Fistula Remission

Secondary endpoints



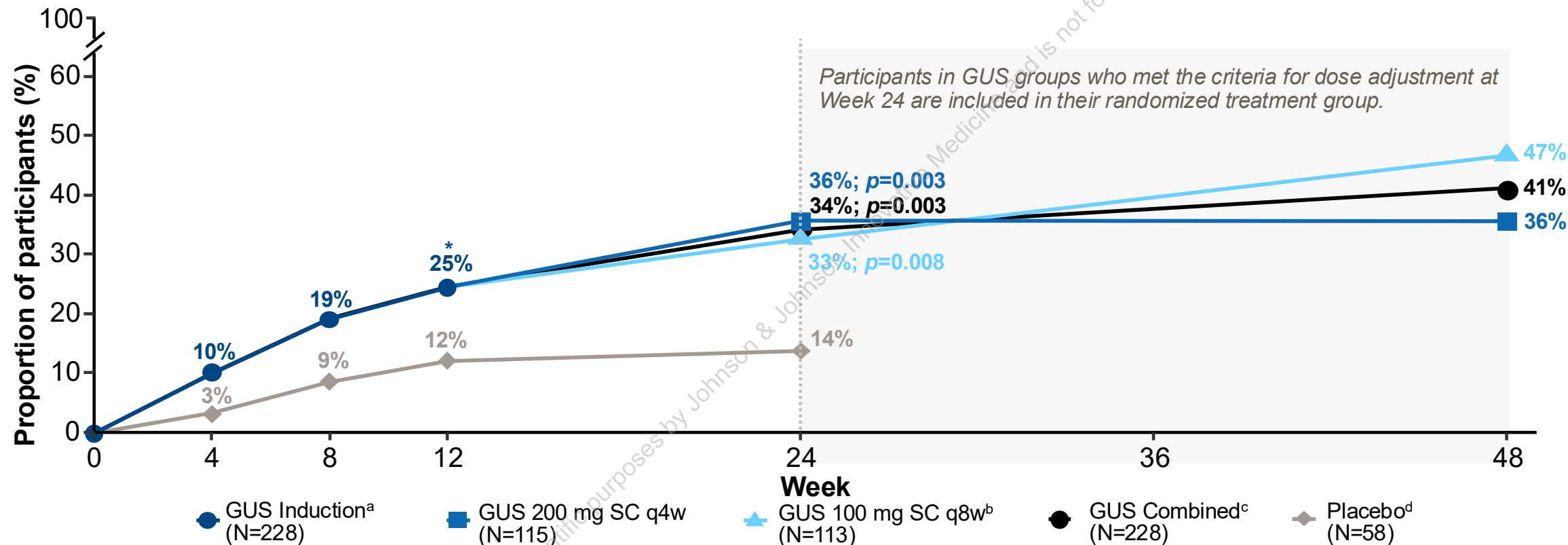
p -values are multiplicity-controlled, except for GUS combined (nominal).

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

After applying the intercurrent event strategy in the statistical analysis, missing data were imputed as not having achieved binary endpoints. ^aGUS 200 mg IV induction at W0/4/8. ^bAt Week 48, GUS 100 mg SC q8w group includes participants on 100 mg SC q8w (R), and those (NRs) with dose adjusted to 200 mg SC q4w at W24. ^cGUS combined included both maintenance dose arms from Week 12 through Week 48. ^dNR placebo participants received blinded GUS dose adjustment after Week 24, thus, there is no more placebo arm after Week 24. **GUS**=guselkumab, **IV**=intravenous, **NR**=non-responders, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **R**=responders, **SC**=subcutaneous.

Clinically Assessed Fistula Response

Secondary endpoints



p-values are multiplicity-controlled, except for GUS combined (nominal); *Nominal $p < 0.05$ vs placebo.

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

After applying the intercurrent event strategy in the statistical analysis, missing data were imputed as not having achieved binary endpoints. ^aGUS 200 mg IV induction at W0/4/8. ^bAt Week 48, GUS 100 mg SC q8w group includes participants on 100 mg SC q8w (R), and those (NRs) with dose adjusted to 200 mg SC q4w at W24. ^cGUS combined included both maintenance dose arms from Week 12 through Week 48. ^dNR placebo participants received blinded GUS dose adjustment after Week 24, thus, there is no more placebo arm after Week 24. **GUS**=guselkumab, **IV**=intravenous, **NR**=non-responders, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **R**=responders, **SC**=subcutaneous.

Adverse Events Through Week 48

	GUS 100 mg SC q8w ^a (N=113)	GUS 200 mg SC q4w ^a (N=115)	GUS Combined ^a (N=228)	All GUS ^b (N=268)	Placebo ^a (N=58)
Mean duration of follow-up (weeks)	33.6	33.6	33.6	42.8	28.7
Mean exposure (number of study agent administrations)	8.4	8.5	8.4	11.3	6.9
Subjects with ≥1 Adverse events	80 (71%)	88 (77%)	168 (74%)	216 (81%)	48 (83%)
Subjects with ≥1 Serious adverse events	18 (16%)	9 (8%)	27 (12%)	34 (13%)	8 (14%)
Subjects with ≥1 Adverse events leading to study agent discontinuation	8 (7%)	5 (4%)	13 (6%)	16 (6%)	5 (9%)
Subjects with ≥1 Infection	52 (46%)	41 (36%)	93 (41%)	126 (47%)	28 (48%)
Subjects with ≥1 Anal abscess	13 (12%)	6 (5%)	19 (8%)	26 (10%)	3 (5%)
Subjects with ≥1 Serious infection	13 (12%)	2 (2%)	15 (7%)	17 (6%)	2 (3%)
Subjects with ≥1 Serious gastrointestinal disorders	5 (4%)	3 (3%)	8 (4%)	10 (4%)	4 (7%)

- GUS was well tolerated through Week 48, with overall adverse event rates similar to placebo with both doses
- Two participants with malignancies (plasmablastic lymphoma and NMSC) were reported in the GUS 200 mg group, which were assessed as unrelated to study intervention by investigator
- No reported cases of additional AEs of interest (anaphylactic reactions, opportunistic infections, major adverse cardiovascular events, venous thromboembolisms, active tuberculosis, or clinically important hepatic disorders)

Data shown are n (%) unless otherwise noted. ^aExcludes data from Week 24 to Week 48 of participants who were dose adjusted to GUS 200 mg q4w at Week 24. ^bIncludes data for participants who received at least one dose of GUS, covering the period from their first GUS dose through Week 48. **GUS**=guselkumab, **NMSC**=non-melanoma skin cancer, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous.

Key Takeaways

- ✓ FUZION is the first large international Phase 3 study dedicated to perianal fistulizing Crohn's disease in more than two decades that showed efficacy of an advanced therapy
- ✓ GUS showed superior efficacy to placebo at Week 24
- ✓ GUS demonstrated sustained efficacy through Week 48, supporting its continued use for durable fistula remission
- ✓ GUS was well tolerated through Week 48, with no new safety signals identified

Backup slides

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Maintenance of fistula remission and response through Week 48

Among participants randomized to GUS who achieved the respective endpoints at Week 24:

- 70% maintained **combined fistula remission** through Week 48
- 71% maintained **clinically assessed fistula remission** through Week 48
- 76% maintained **clinically assessed fistula response** through Week 48

Adverse Events in Dose Adjusted Participants From Week 24 to Week 48

	From Week 24 to Week 48 ^a		
	GUS 100 mg SC q8w -> GUS 200 mg SC q4w (N=55)	GUS 200 mg SC q4w -> GUS 200 mg SC q4w (N=67)	Placebo -> GUS 200 mg SC q4w (N=40)
Mean duration of follow-up (weeks)	23.9	23.4	23.1
Mean exposure (number of study agent administrations)	6.9	6.6	6.8
Subjects with ≥1 Adverse events	36 (65%)	44 (66%)	26 (65%)
Subjects with ≥1 Serious adverse events	4 (7%)	4 (6%)	1 (2%)
Subjects with ≥1 Adverse events leading to study agent discontinuation	1 (2%)	1 (1%)	1 (2%)
Subjects with ≥1 Infection	17 (31%)	25 (37%)	8 (20%)
Subjects with ≥1 Anal abscess	4 (7%)	4 (6%)	0
Subjects with ≥1 Serious infection	2 (4%)	1 (1%)	0
Subjects with ≥1 Serious gastrointestinal disorders	1 (2%)	0	1(2%)