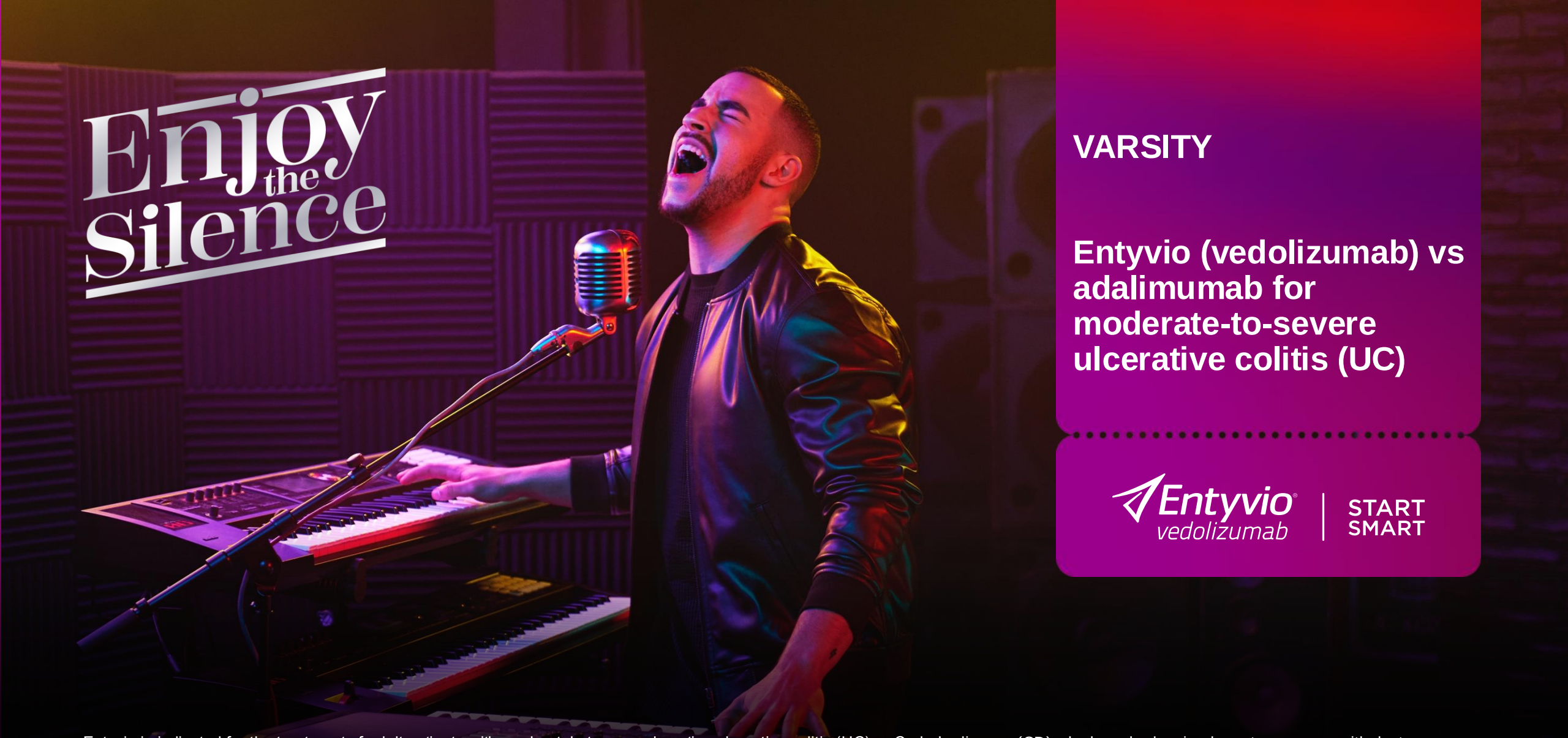


VARSITY

Entyvio (vedolizumab) vs adalimumab for moderate-to-severe ulcerative colitis (UC)

Entyvio® vedolizumab | START SMART

Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF) antagonist. Entyvio is also indicated for the treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone protocolectomy and ileal pouch anal anastomosis for UC and have had an inadequate response with or lost response to antibiotic therapy.

Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

C-APROM/IE/ENTUC/0007 | June 2024

Takeda

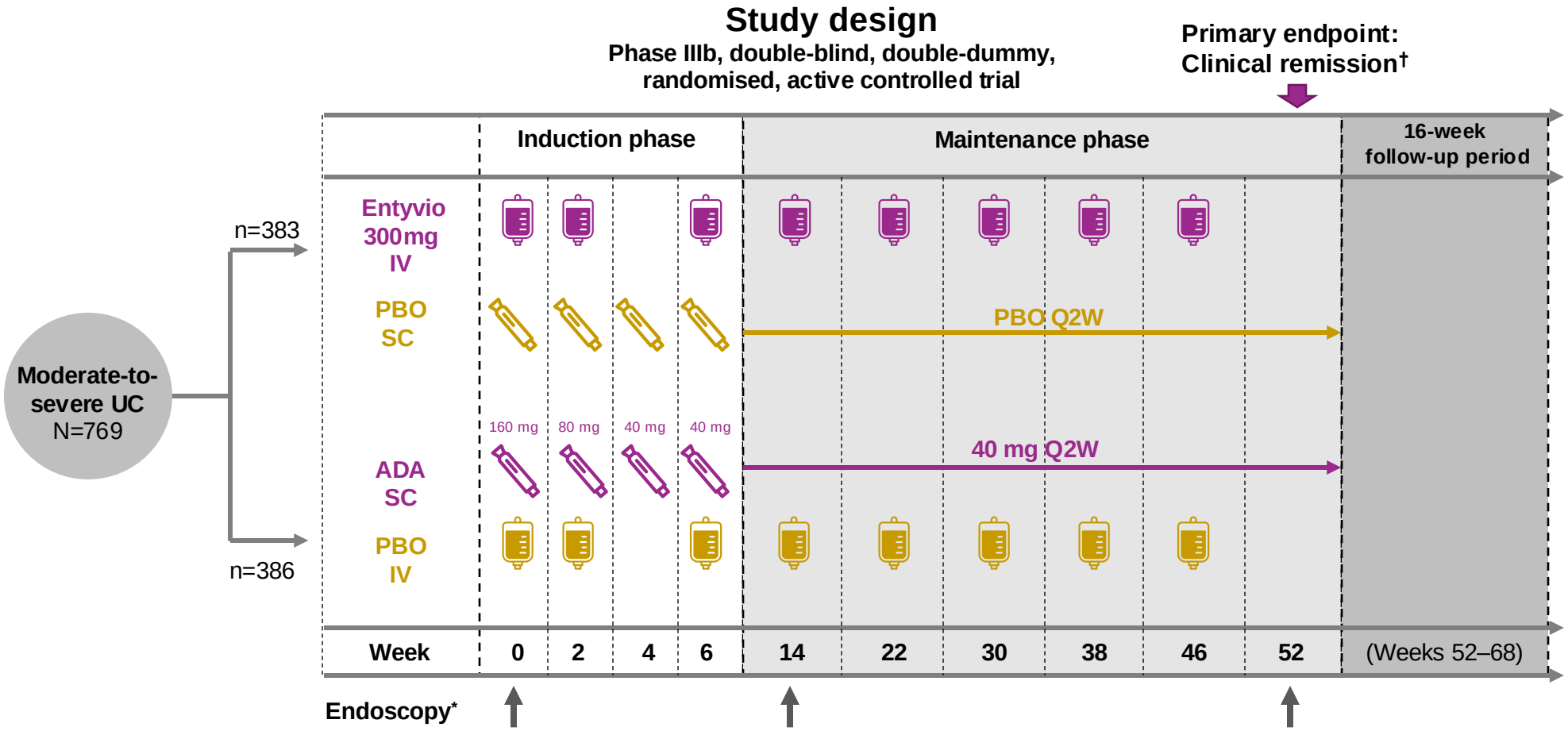
The first head-to-head trial evaluating the efficacy and safety of Entyvio (vedolizumab) with adalimumab in patients with moderately-to-severely active ulcerative colitis

Patients enrolled in the study had failed conventional therapies and were either biologic-naïve or anti-TNFα failure patients. Patients who had discontinued treatment with a TNF inhibitor (except adalimumab) because of documented reasons other than safety were also eligible, with enrolment capped at

TNF, tumour necrosis factor.

Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

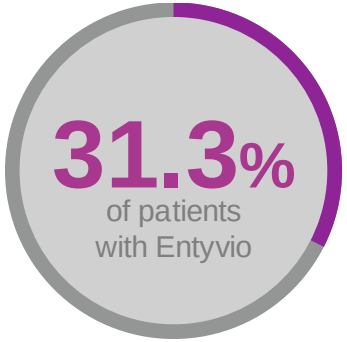
The first head-to-head trial evaluating the efficacy and safety of Entyvio (vedolizumab) with adalimumab in patients with moderately-to-severely active ulcerative colitis[1,2]

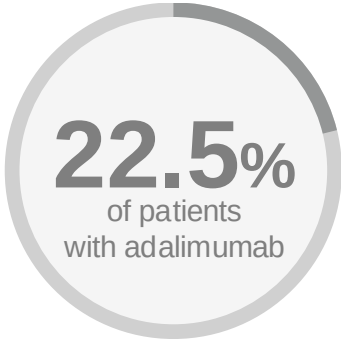


*Endoscopy at baseline, Week 14 and Week 52. †The primary endpoint was clinical remission, defined as a complete Mayo score ≤2 and no individual subscore >1, at Week 52.
ADA, adalimumab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; SC, subcutaneous; TNF, tumour necrosis factor; UC, ulcerative colitis.
1. NCT02497467. Available at: clinicaltrials.gov/ct2/show/NCT02497469. Accessed May 2024; 2. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

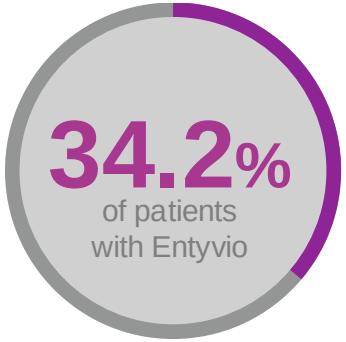
Statistically more patients treated with Entyvio were in clinical remission vs adalimumab at Week 52[1]

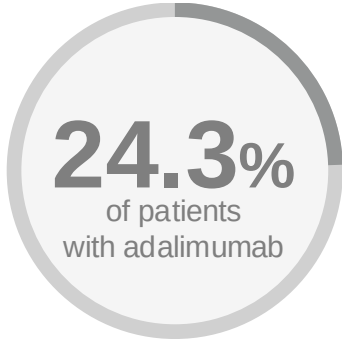
In the overall population, clinical remission at Week 52 was observed in:



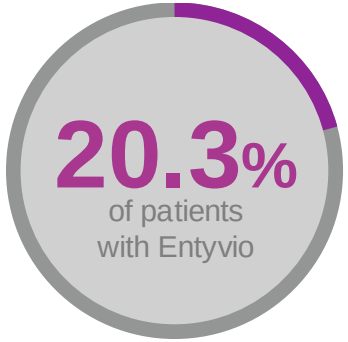


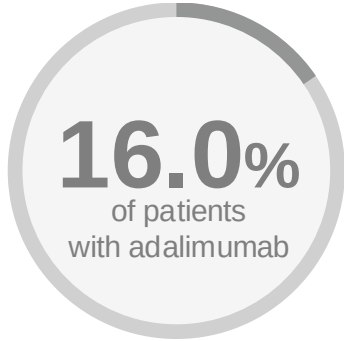
Among the patients who did not have previous exposure to a TNF inhibitor (Entyvio n=305; adalimumab n=305), clinical remission at Week 52 was observed in:





Among the patients who had previous exposure to a TNF inhibitor other than adalimumab (Entyvio n=80; adalimumab n=81), clinical remission at Week 52 was observed in:





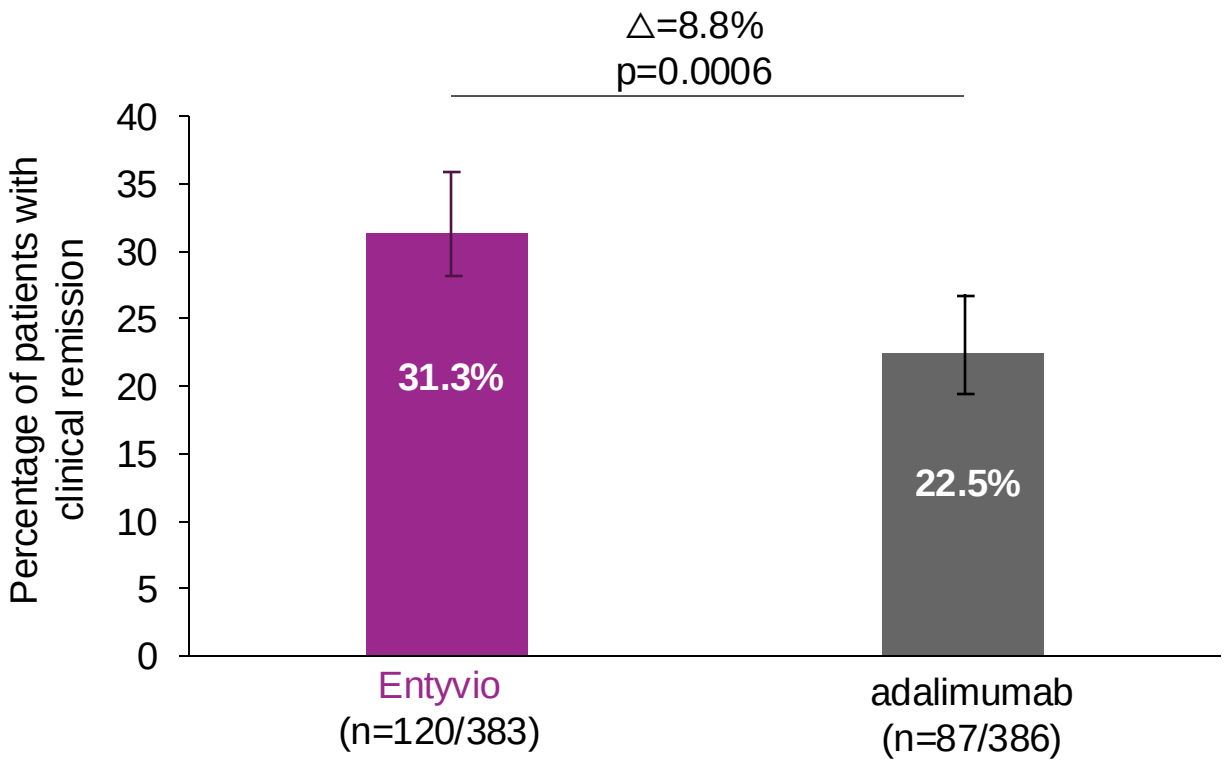
TNF, tumour necrosis factor.

1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

Statistically more patients treated with Entyvio were in clinical remission vs adalimumab at Week 52[1]

Primary endpoint:

Clinical remission* in moderate-to-severe patients with UC at Week 52

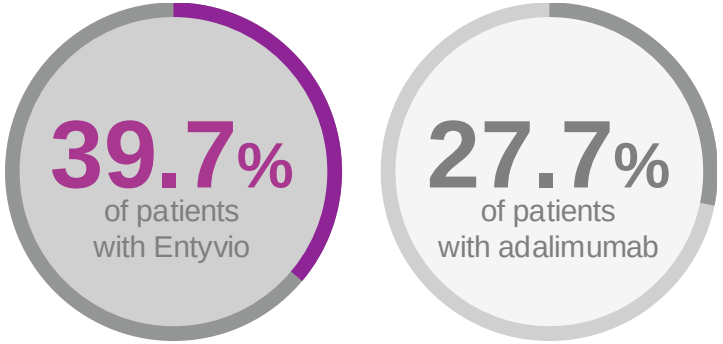


*Defined as a complete Mayo score ≤2 and no individual subscore >1.
UC, ulcerative colitis.

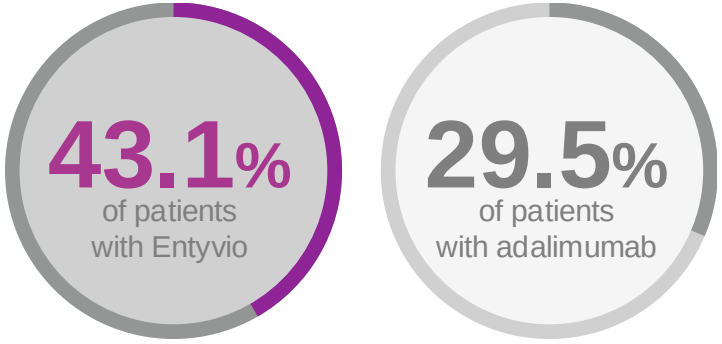
1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

Entyvio achieved significantly higher rates of mucosal healing vs adalimumab at Week 52[1]

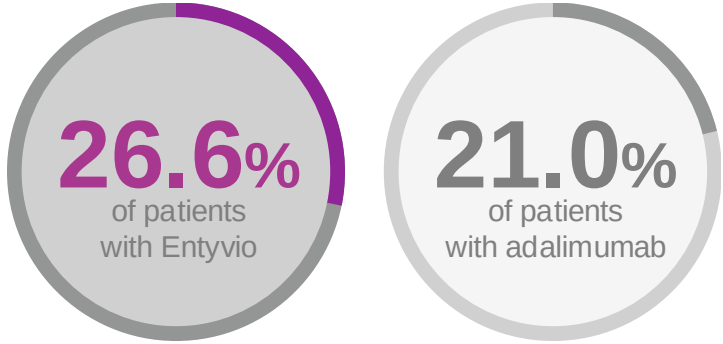
In the overall population, mucosal healing at Week 52 was observed in:



Among the patients who did not have previous exposure to a TNF inhibitor (Entyvio n=305; adalimumab n=305), mucosal healing at Week 52 was observed in:



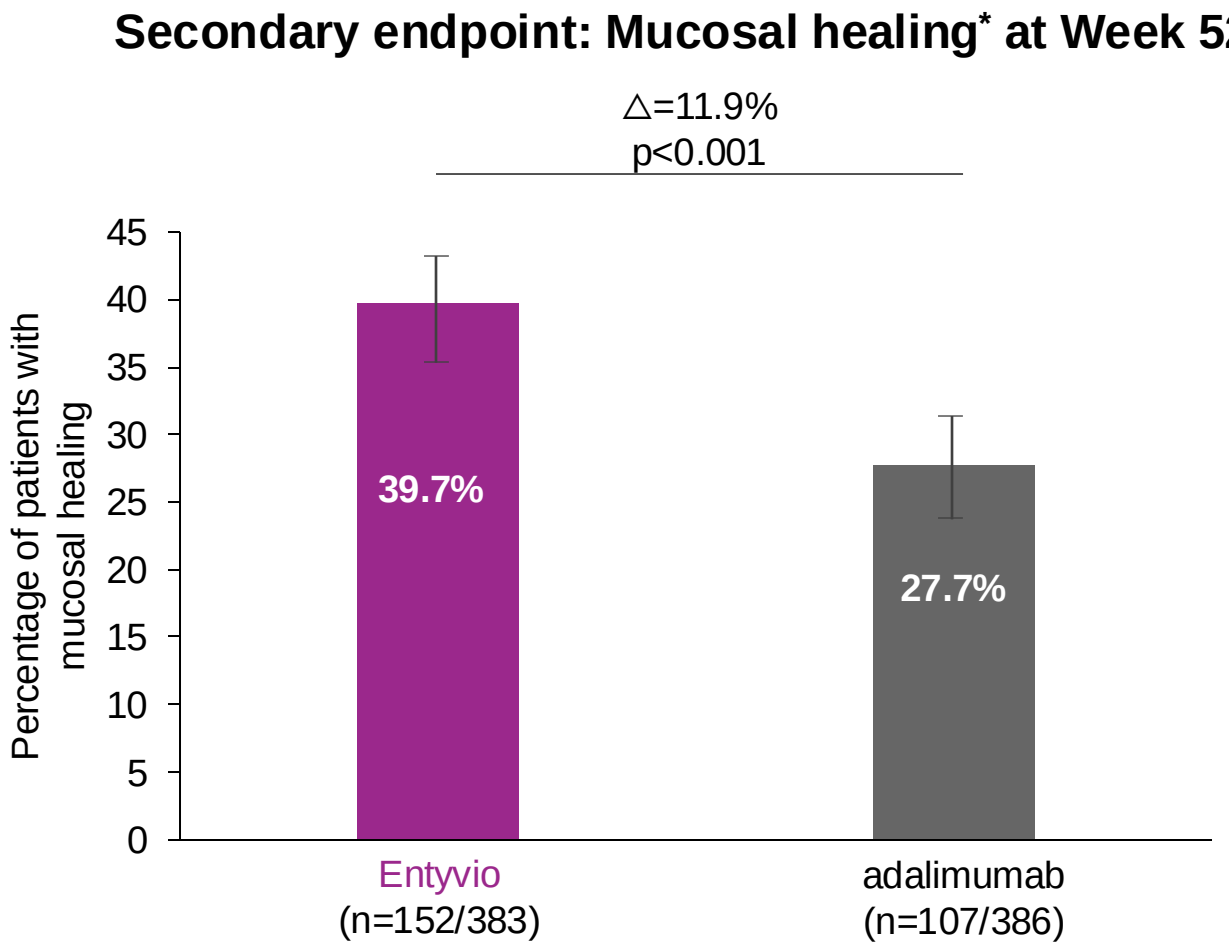
Among the patients who had previous exposure to a TNF inhibitor other than adalimumab (Entyvio n=80; adalimumab n=81), mucosal healing at Week 52 was observed in:



TNF, tumour necrosis factor.

1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

Entyvio achieved significantly higher rates of mucosal healing vs adalimumab at Week 52[1]



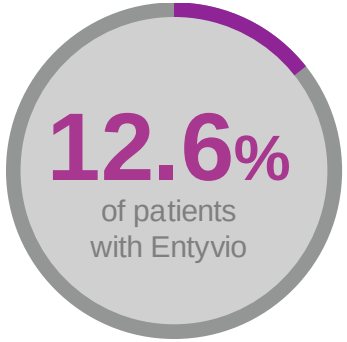
*Defined as a subscore of 0 or 1 on the Mayo endoscopic component.

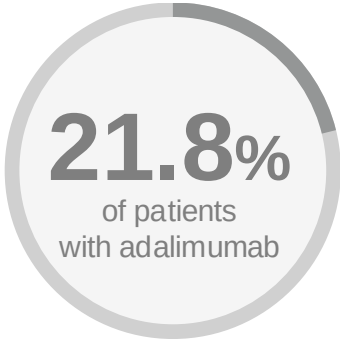
1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

Absolute reduction in steroid use was greater with Entyvio than adalimumab, but no significant treatment differences were observed in steroid free remission[1]

At baseline, 139 patients in the Entyvio arm and 140 patients in the adalimumab arm were receiving corticosteroids

The rates of corticosteroid free remission* were:





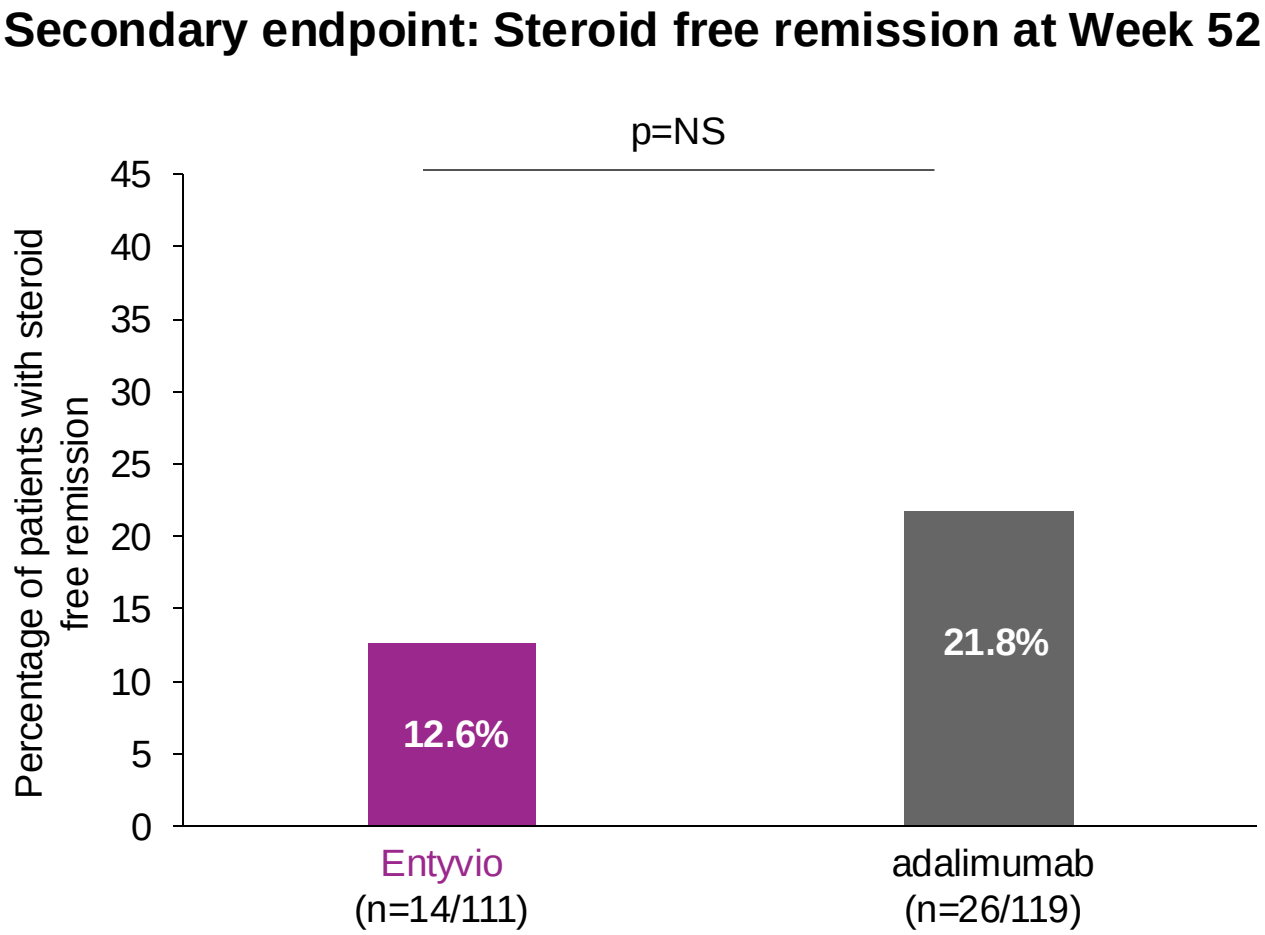
The median change in the oral corticosteroid dose from baseline to Week 52 was:

The median corticosteroid dose at Week 52 was:

*Corticosteroid free remission was defined as as participants using oral corticosteroids at Baseline (Week 0) who had discontinued oral corticosteroids and were in clinical remission at Week 52.[2] Clinical remission was defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point.[2]

1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226; 2. NCT02497467. Available at: clinicaltrials.gov/ct2/show/NCT02497469. Accessed May 2024.

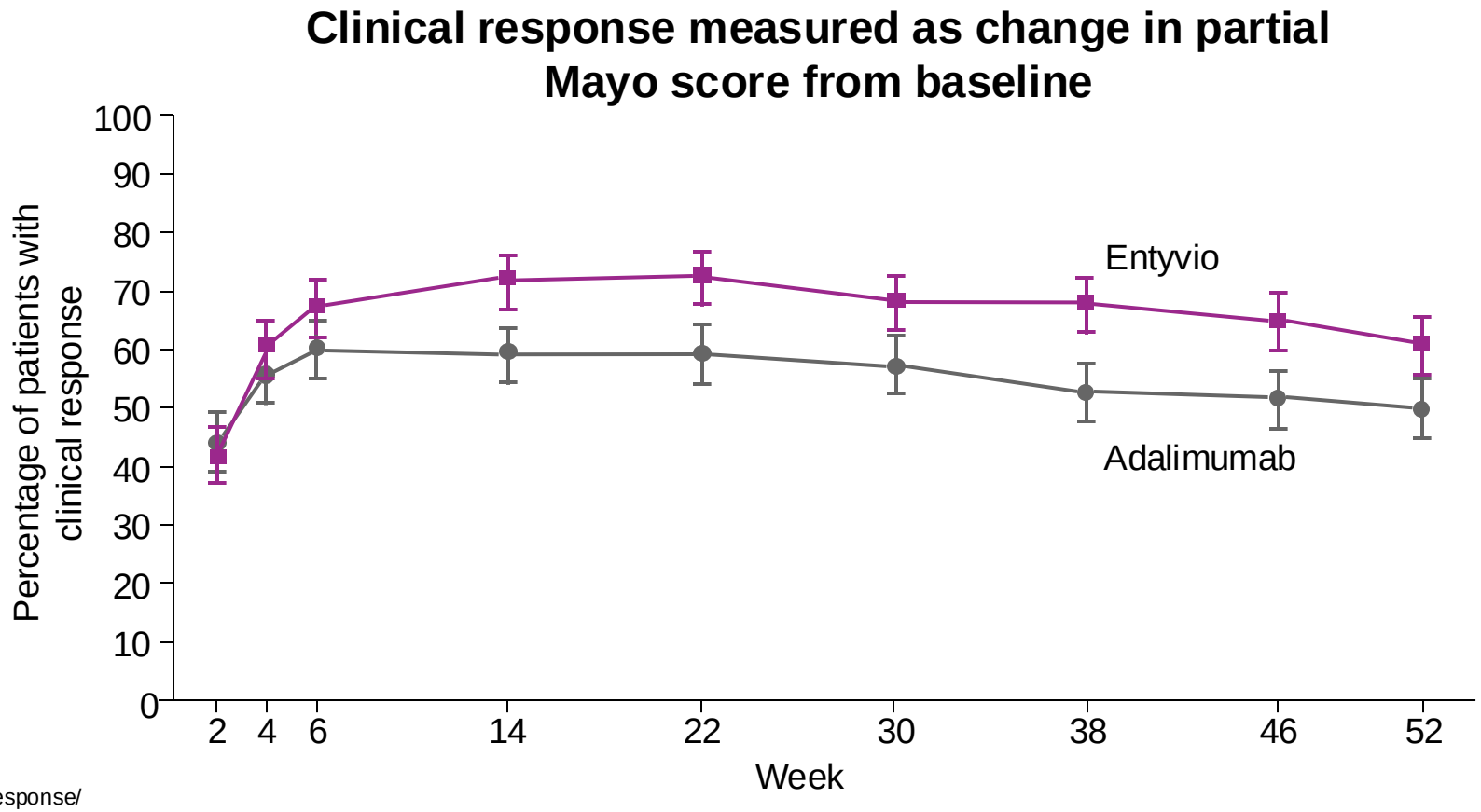
Absolute reduction in steroid use was greater with Entyvio than adalimumab, but no significant treatment differences were observed in steroid free remission[1]



NS, not significant.

1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

Entyvio delivered a similar speed of clinical response* as adalimumab at Weeks 2–6[1]

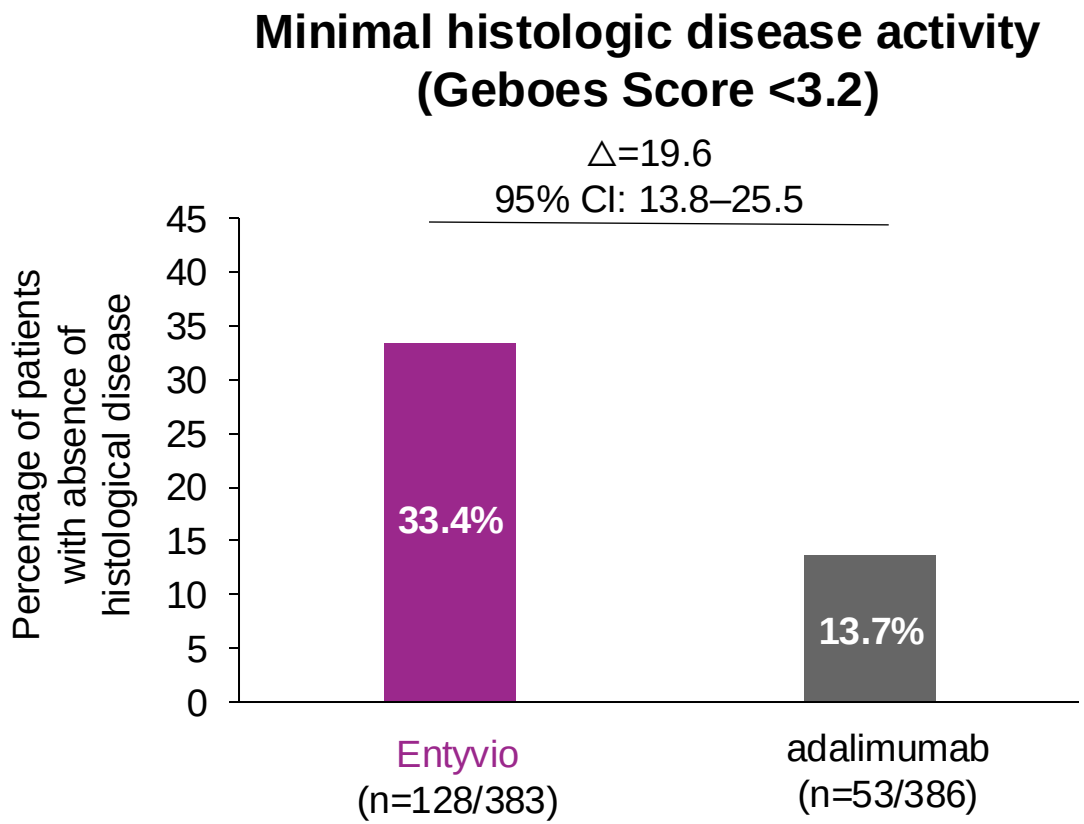


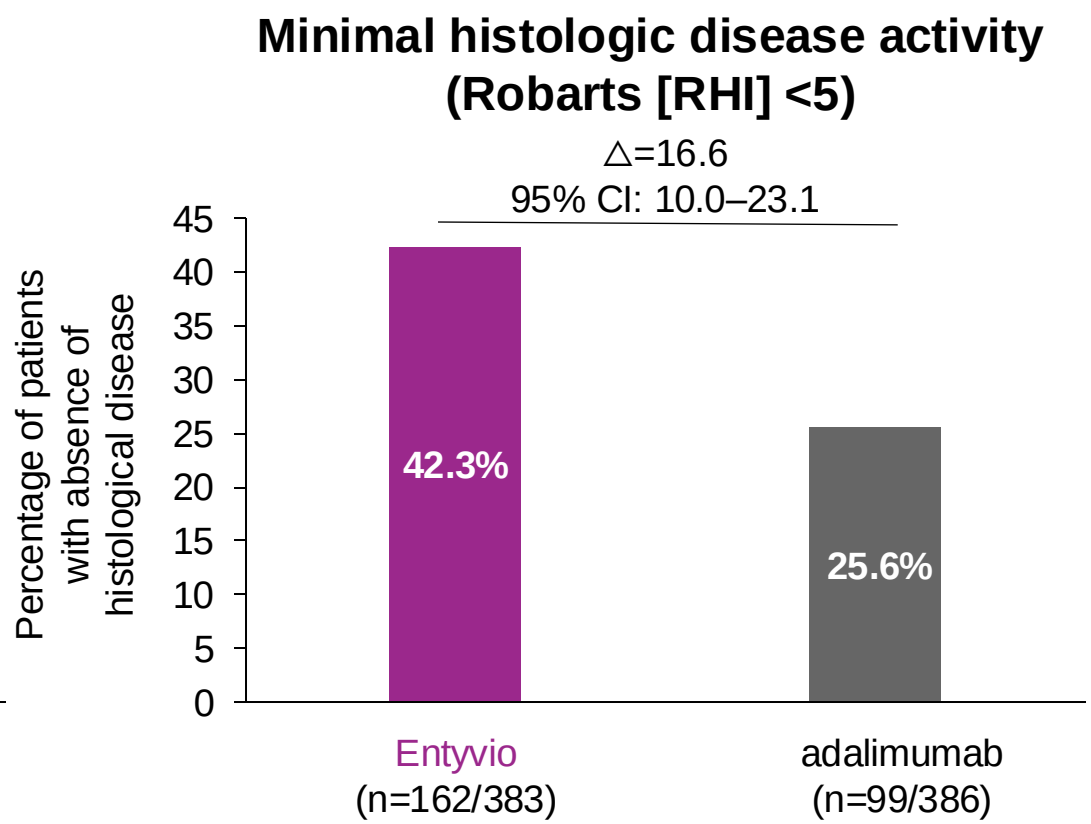
Patients with Clinical Response/ Patients with Available Data									
Entyvio (n=383)	161/367	233/357	263/356	276/344	278/325	262/298	263/293	251/280	233/265
Adalimumab (n=386)	176/374	217/366	232/364	229/342	229/295	222/270	206/245	200/228	193/221

*The assessment of clinical response was based on the change in the partial score on the Mayo scale from baseline to trial visit. A clinical response was defined as a reduction in the partial Mayo score of at least 2 points and of at least a 25% from baseline, with an accompanying decrease of at least 1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1.

1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

Entyvio was superior to adalimumab in achieving minimal histologic disease activity at Week 52 in ulcerative colitis[1]



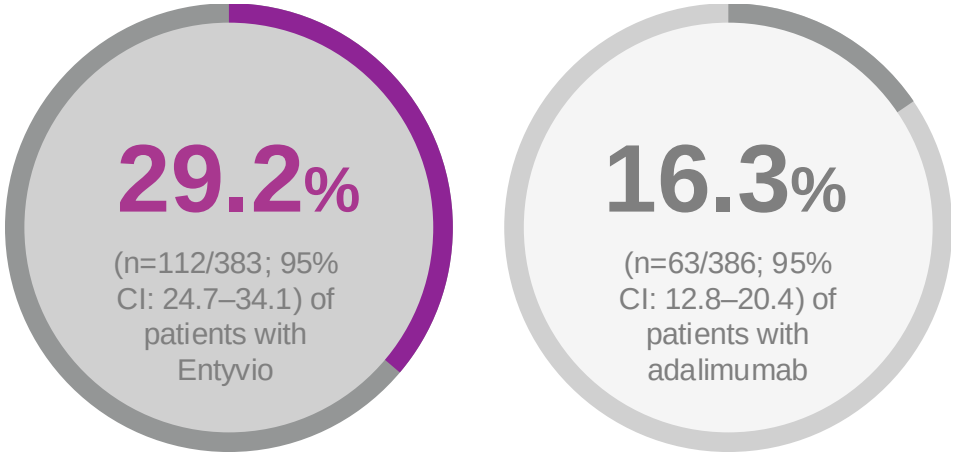


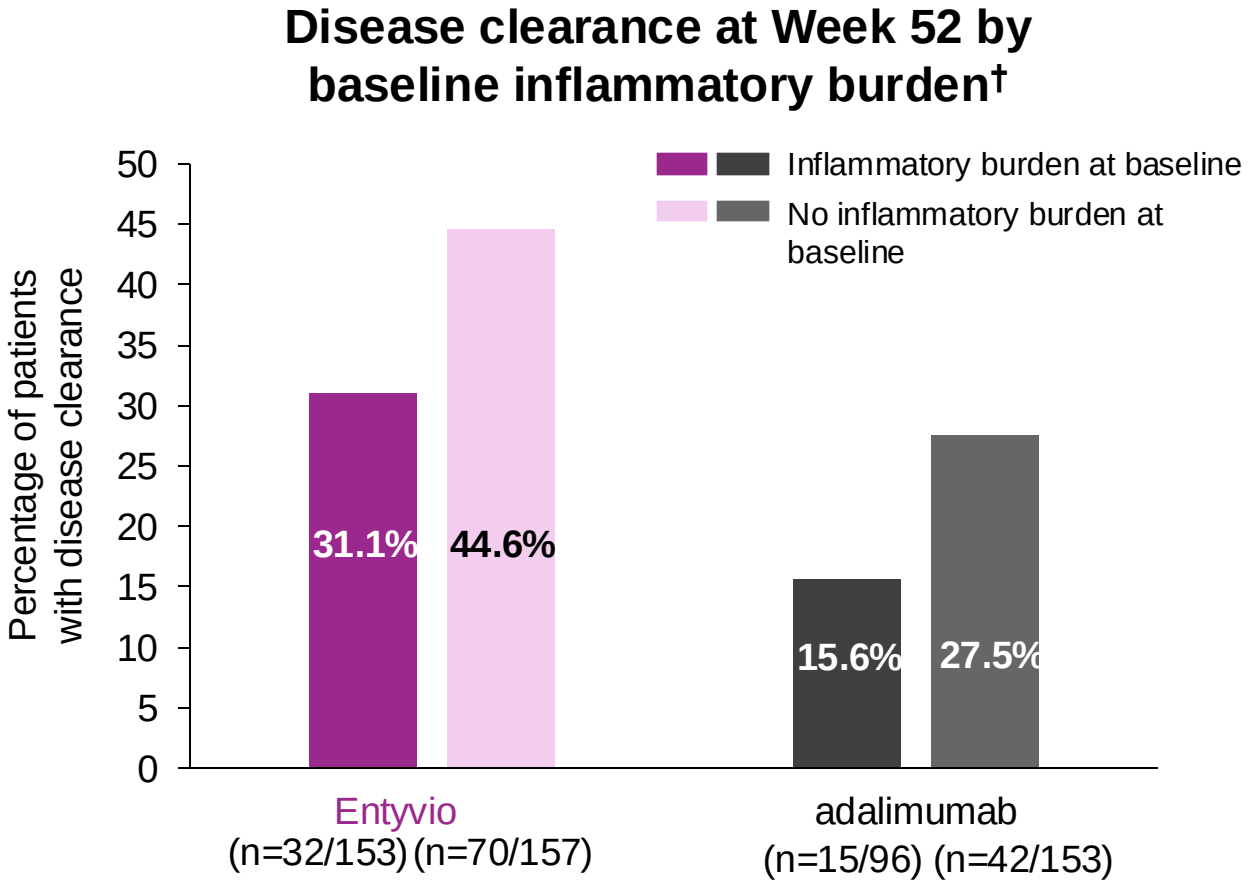
Full analysis set includes all randomised patients who received at least 1 dose of study drug. Patients with missing data to determine outcome were considered non-responders.
RHI, Robarts Histopathology Index.

1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226. Supplementary appendix.

More patients treated with Entyvio achieved disease clearance* at Week 52 than those treated with adalimumab[1]

More patients in the Entyvio treatment group than the adalimumab group achieved disease clearance at Week 52:





*Disease clearance was defined as a composite outcome based on clinical remission (partial Mayo score ≤2 and no individual subscore >1 excluding sigmoidoscopy subscore), endoscopic improvement (endoscopic subscore ≤1) and absence of active histologic disease (minimum histological disease activity; Robarts Histology Index [RHI] <5).
†Inflammatory burden defined at C-reactive protein ≥5 mg/L and fecal calprotectin >100 µg/g.
CI, confidence interval.
1. Danese S, et al. *J Crohns Colitis* 2021;15(Suppl 1):S305.

The majority of adverse events in VARSITY were mild to moderate[1]

Incidence of AEs and SAEs (safety population)*

	Entyvio (n=383)	Adalimumab (n=386)
Any AE, n (%)	240 (62.7%)	267 (69.2%)
Mild, n (%)	111 (29.0%)	118 (30.6%)
Moderate, n (%)	92 (24.0)	109 (28.2%)
Severe, n (%)	37 (9.7%)	40 (10.4%)
SAE, n (%)	42 (11.0%)	53 (13.7%)
Exposure-adjusted infection rate, incidence rate/100 patient years	23.4	34.6

- Few infections were considered serious in either group

*The safety population was defined as all patient who received at least one dose of a trial medicine.
AE, adverse event; SAE, serious adverse event.
1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226.

Entyvio demonstrated a comparable safety profile to adalimumab

Most frequent AEs (safety population)*

Event, n (%)	Entyvio (n=383)	Adalimumab (n=386)
≥1 AE	126 (32.9)	138 (35.8)
Ulcerative colitis	44 (11.5)	63 (16.3)
Nasopharyngitis	27 (7.0)	30 (7.8)
Headache	27 (7.0)	21 (5.4)
Anaemia	20 (5.2)	26 (6.7)
Abdominal pain	18 (4.7)	20 (5.2)
Upper respiratory tract infection	20 (5.2)	17 (4.4)

*The safety population was defined as all patient who received at least one dose of a trial medicine.
AE, adverse event.
1. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226. Supplementary appendix.

Discussion points and points of interest

- VARSITY was the first head-to-head trial evaluating the efficacy and safety of Entyvio (vedolizumab) with adalimumab in patients with moderately-to-severely active ulcerative colitis[1,2]
- Entyvio demonstrated statistically significant superior rates of clinical remission (**31.3%** vs **22.5%**; p<0.001) and mucosal healing (**39.7%** vs **27.7%**; p<0.001) vs adalimumab at Week 52[2]
- Absolute reduction in steroid use was greater with Entyvio than adalimumab, but no significant difference was observed in corticosteroid free remission between the two groups[2]
- Entyvio delivered a similar speed of response as adalimumab at Weeks 2–6[2]
- Entyvio was superior to adalimumab in minimal histologic disease activity at Week 52 in ulcerative colitis[3]
- Geboes Score <3.2: **33.4%** with Entyvio vs **13.7% with adalimumab**
- Robarts (RHI) <5: **42.3%** with Entyvio vs **25.6% with adalimumab**
- More patients treated with Entyvio achieved disease clearance at week 52 than those treated with adalimumab (**29.2%** vs **16.3%**)[4]
- Entyvio demonstrated a comparable safety profile to adalimumab[2,3]

RHI, Robarts Histopathology Index.

1. NCT02497467. Available at: clinicaltrials.gov/ct2/show/NCT02497469. Accessed May 2024; 2. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226; 3. Sands BE, et al. *N Engl J Med* 2019;381:1215–1226. Supplementary appendix; 4. Danese S, et al. *J Crohns Colitis* 2021;15(Suppl 1):S305.

ENTYVIO® (vedolizumab) PRESCRIBING INFORMATION for REPUBLIC OF IRELAND

Refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: **Entyvio intravenous (IV):** 300 mg powder for concentrate for solution for infusion. **Entyvio subcutaneous (S/C):** 108 mg solution for injection in pre-filled pen. **Indication:** **Entyvio IV and Entyvio S/C:** Adult patients with moderately to severely active ulcerative colitis (UC)/Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. **Entyvio IV only:** Adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for UC, and have had an inadequate response with or lost response to antibiotic therapy. **Dosage and administration:** Treatment should be initiated and supervised by a specialist healthcare professional experienced in diagnosis and treatment of UC, CD or pouchitis. **Entyvio IV:** Patients should be monitored during and after infusion in a setting equipped to manage anaphylaxis. UC: Recommended dose regimen 300 mg administered by IV infusion over 30 minutes at 0, 2, 6 weeks and every 8 weeks thereafter. Discontinue treatment if no evidence of therapeutic benefit by week 10. If patients experience a decrease in response, they may benefit from increased dosage frequency to 300 mg every 4 weeks. Corticosteroids may be reduced/discontinued in patients who respond to treatment with Entyvio. If therapy is interrupted and needs to be restarted, Entyvio dosing every 4 weeks may be considered. CD: Recommended dose regimen is 300 mg administered by IV infusion over 30 minutes at 0, 2, 6 weeks and every 8 weeks thereafter. Patients who have not shown evidence of therapeutic benefit may benefit from a dose at week 10. Continue therapy every 8 weeks from week 14 in responding patients. Therapy should be discontinued if no evidence of therapeutic benefit is observed by week 14. If therapy is interrupted and needs to be restarted, Entyvio dosing every 4 weeks may be considered. Pouchitis: Recommended dose regimen is 300 mg administered by IV infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Treatment should be initiated in parallel with standard of care antibiotic (e.g., four-week of ciprofloxacin). Therapy discontinuation should be considered if no evidence of therapeutic benefit is observed by week 14. There are no retreatment data available if therapy is interrupted and needs to be restarted. **Entyvio S/C:** UC and CD: Recommended dose regimen, following at least two IV infusions, is 108mg administered by subcutaneous injection once every 2 weeks. The first S/C dose should be administered in place of the next scheduled IV dose and every 2 weeks thereafter. Insufficient data to determine if patients who experience a decrease in response on maintenance treatment with Entyvio S/C would benefit from an increase in dosing frequency. No data on transition of patients from Entyvio S/C to Entyvio IV during maintenance therapy. Paediatric populations: No data available in children aged 0-17 years. Not recommended. Elderly patients: No dosage adjustment required. Renal or hepatic impairment: Entyvio has not been studied in these populations. No dose recommendation can be given. **Contraindications:** Hypersensitivity to Entyvio or any of the excipients. Active severe infections such as tuberculosis (TB), sepsis, cytomegalovirus, listeriosis and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML). **Warnings and precautions:** Entyvio IV: Patients should be observed continuously during infusions for signs/symptoms of hypersensitivity reactions. Patients should continue to be observed for two hours following infusion completion for the first two infusions and one hour for subsequent infusions. Infusion-related reactions (IRR): Hypersensitivity reactions have been reported, the majority were of mild to moderate severity. Discontinue treatment if anaphylaxis or other serious allergic reactions occur and initiate appropriate treatment. In mild to moderate IRR, slow or interrupt infusion. Consideration for pre-treatment with antihistamine, hydrocortisone and/or paracetamol should be given prior to next infusion, for patients with history of mild/moderate IRR to Entyvio. **Entyvio IV and Entyvio S/C:** Infections: Not recommended in patients with active, severe infections until infections are controlled. Consider withholding in patients who develop severe infection while on treatment with Entyvio. Before initiating treatment, patients must be screened for TB. If latent TB is diagnosed, anti-tuberculosis appropriate treatment must be initiated prior to Entyvio treatment. Progressive Multifocal Leukoencephalopathy (PML): John Cunningham (JC) virus infection resulting in PML and death has occurred in patients treated with other integrin receptor antagonists and systemic immunosuppressive agents. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs/symptoms. Malignancy: Underlying increased risk of malignancy in UC and CD. Immunomodulatory products may increase risk. Prior and concurrent use of biological products: No clinical data available for Entyvio use in patients previously treated with natalizumab or rituximab. Patients previously exposed to natalizumab should wait at least 12 weeks prior to initiating Entyvio therapy. Entyvio not recommended for concomitant use with biologic immunosuppressants as no clinical data available. Live and oral vaccines: Patients may continue to receive non-live vaccines. Patients recommended to be up-to-date with all appropriate immunisations prior to initiating Entyvio. Live vaccines may be administered concurrently only if benefit clearly outweighs risk. **Interactions:** No interaction studies performed. UC and CD: Concomitant administration of corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) and aminosalicylates did not have a clinically meaningful effect on Entyvio pharmacokinetics. Pouchitis: Concomitant administration of antibiotics have been observed. The effect on the pharmacokinetics of commonly co-administered medicinal compounds has not been studied. **Fertility, pregnancy and lactation:** There are no data on the effects of vedolizumab on human fertility. Women of childbearing potential should use adequate contraception and continue for at least 18 weeks after last Entyvio treatment. Preferable to avoid use of Entyvio during pregnancy unless benefits clearly outweigh potential risk to both the mother and foetus. Entyvio has been detected in human milk. The effects on breast-fed infants and milk production are unknown. Use of Entyvio in lactating women should consider the benefit of therapy against potential risks to the infant. **Undesirable effects:** No clinically relevant differences in overall safety profile and adverse reactions observed in patients who received Entyvio S/C compared with Entyvio IV except for injection site reactions (with S/C administration). Very Common (≥1/10): nasopharyngitis, headache, arthralgia. Common (≥1/100, <1/10): injection site reactions (Entyvio S/C only), pneumonia, Clostridium difficile infection, bronchitis, gastroenteritis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, herpes zoster, paraesthesia, hypertension, oropharyngeal pain, nasal congestion, cough, anal abscess, anal fissure, nausea, dyspepsia, constipation, abdominal distension, flatulence, haemorrhoids, rectal haemorrhage*, rash, pruritus, eczema, erythema, night sweats, acne, muscle spasm, back pain, muscular weakness, fatigue, pain in extremity, pyrexia, infusion related reaction (asthenia* and chest discomfort*), infusion site reaction (including: infusion site pain and infusion site irritation). *Reported in the EARNEST pouchitis study. Uncommon (≥ 1/1,000 to < 1/100): respiratory tract infection, blurred vision. Very rare (< 1/10,000): anaphylactic reaction, anaphylactic shock. Not known: interstitial lung disease. **Refer to the SmPC for details on full side effect profile and interactions.** **Legal Classification:** POM. **Marketing authorisation (MA):** **Entyvio IV:** EU/1/14/923/001. **Entyvio S/C:** EU/1/14/923/005. **Name and Address of MA holder:** Takeda Pharma A/S, Delta Park 45, 2665 Vallensbaek Strand, Denmark. Additional information is available on request at: medinfoemea@takeda.com. **PI Approval Code:** pi-02511. **Date of revision:** July 2023.

Adverse Events should be reported to the Pharmacovigilance Unit at the Health Products Regulatory Authority. Reporting forms and information can be found at: www.hpra.ie. Adverse events should also be reported to Takeda at: AE.GBR-IRL@takeda.com.

Entyvio® vedolizumab | START SMART