

Determining the optimal treatment target in patients with ulcerative colitis: rationale, design, protocol and interim analysis for the randomised controlled VERDICT trial

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ABSTRACT

Introduction Symptoms, endoscopy and histology have been proposed as therapeutic targets in ulcerative colitis (UC). Observational studies suggest that the achievement of histologic remission may be associated with a lower risk of complications, compared with the achievement of endoscopic remission alone. The active ulcerative colitis, a Randomised Controlled Trial (VERDICT) aims to determine the optimal treatment target in patients with UC.

Methods and analysis In this multicentre, prospective randomised study, 660 patients with moderate to severe UC (Mayo rectal bleeding subscore [RBS] ≥ 1 ; Mayo endoscopic score [MES] ≥ 2) are randomly assigned to three treatment targets: corticosteroid-free symptomatic remission (Mayo RBS=0) (group 1); corticosteroid-free endoscopic remission (MES ≤ 1) and symptomatic remission (group 2); or corticosteroid-free histologic remission (Geboes score $< 2B.0$), endoscopic remission and symptomatic remission (group 3). Treatment is escalated using vedolizumab according to a treatment algorithm that is dependent on the patient's baseline UC therapy until the target is achieved at weeks 16, 32 or 48. The primary outcome, the time from target achievement to a UC-related complication, will be compared between groups 1 and 3 using a Cox proportional hazards model.

Ethics and dissemination The study was approved by ethics committees at the country level or at individual sites as per individual country requirements. A full list of ethics committees is available on request. Study results will be disseminated in peer-reviewed journals and at scientific meetings.

Trial registration number EudraCT: 2019-002485-12; NCT04259138.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Disease activity and response to therapy in ulcerative colitis (UC) are assessed through the evaluation of symptoms, endoscopy, histology and biomarkers; however, the optimal treatment target is uncertain. Histologic remission may be a distinct treatment target, with observational studies demonstrating a lower risk of complications after histologic remission compared with endoscopic remission alone. In addition, histologic disease activity can persist in approximately 25% of patients with normal-appearing mucosa.

WHAT THIS STUDY ADDS

⇒ The active ulcerative colitis, a Randomised Controlled Trial (VERDICT) aims to determine whether the achievement of symptomatic, endoscopic and histologic remission is the optimal treatment target for patients with moderately to severely active UC. The interim analysis reported here suggests the feasibility of achieving this target.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study is designed to determine the optimal treatment target in UC, which in turn will help to inform clinical practice, drug development and future evidence-based recommendations aiming to minimise long-term complications and relapse.

INTRODUCTION

Ulcerative colitis (UC) is a chronic and disabling disorder that may progress without appropriate disease modification.¹

Therapeutic goals include reduced disease activity and the prevention of disease progression and complications.² Disease activity and response to therapy in UC can be assessed by a range of endpoints including symptoms, endoscopic mucosal activity, histologic disease activity and biomarkers. Within the same patient, however, considerable discordance exists between these endpoints. Symptoms inherently have a degree of subjectivity and, if used alone for therapeutic decision-making, may lead to undertreatment or overtreatment of disease. Accordingly, consensus recommendations that define treatment targets in UC acknowledge that the resolution of symptoms is not a sufficient treatment target and that objective evaluation of inflammation of the mucosa by endoscopy is necessary.^{3,4} However, it should be recognised that this recommendation is based on expert guidance in the absence of any controlled data to confirm that endoscopic remission is superior to the resolution of symptoms as a treatment target. Nevertheless, the achievement of endoscopic remission is associated with lower rates of relapse, hospitalisation, colectomy and cancer.⁵⁻⁷ Furthermore, in newly diagnosed patients with UC at up to 5 years of follow-up, the achievement of both clinical (symptomatic) and endoscopic remission is associated with reduced rates of relapse, hospitalisation and colectomy, relative to the achievement of symptom resolution alone.⁵

While endoscopic mucosal healing is accepted as the treatment target in UC, it is not necessarily the ideal treatment target given the lack of supporting controlled data and long-term follow-up. Importantly, histologic disease activity persists in approximately one-quarter of patients with normal-appearing mucosa and has been shown to predict UC flares.^{6,8} Studies indicate that the achievement of histologic disease remission is strongly associated with a lower risk of corticosteroid use, hospitalisation and colorectal cancer, as compared with the achievement of endoscopic remission alone, suggesting that histologic remission may be a distinct treatment target in UC.^{6,7} These observations have led clinicians to challenge existing concepts of deep remission and to explore whether histologic healing can confer additional prognostic benefits.

Assessments of endoscopic and histologic endpoints in UC are inherently resource intensive, invasive for patients and have associated costs. Despite a body of observational literature suggesting that persistent endoscopic and histologic disease activity is associated with adverse clinical outcomes, no study to date has shown the superiority of prospective treatment to achieve endoscopic or histologic remission over the treatment of symptoms alone. Therefore, these endpoints are unvalidated surrogate outcomes, and the optimal treatment target for UC remains uncertain.^{3,4} There is a need for a randomised controlled trial to help define the optimal treatment target for clinical practice and to help inform regulatory endpoints and targets for drug development.

The randomised controlled VERDICT trial (in active ulcerative colitis, a Randomised Controlled Trial for determination of the optimal treatment target) aims to determine the optimal treatment target in moderately to severely active UC. The design and rationale for the VERDICT trial was reported at the European Crohn's and Colitis Organisation congress in 2023,⁹ and the first interim analysis of treatment target achievement as of 2 November 2022 was reported at the European Crohn's and Colitis Organisation and the Digestive Disease Week congresses in 2023.^{10,11} Here, we report the study design and protocol of the VERDICT trial, including full definitions of all primary and secondary outcomes, and findings from the second interim analysis of treatment target achievement as of 1 March 2023.

METHODS AND ANALYSIS

Study design

In this multicentre, prospective, randomised controlled trial, 660 patients with active UC (defined as a Mayo rectal bleeding subscore [RBS] of ≥ 1 ^{12,13} and a Mayo endoscopic score [MES] ≥ 2 on flexible sigmoidoscopy) are randomly assigned in a 2:3:5 ratio to one of three groups, each with a different treatment target (figure 1). Investigators receive training on the three treatment target groups and study treatment algorithms.

Treatment target groups

Treatment targets are defined as corticosteroid-free symptomatic remission (group 1), corticosteroid-free endoscopic+symptomatic remission (group 2) and corticosteroid-free histologic+endoscopic+symptomatic remission (group 3). Symptomatic remission is defined as a Mayo RBS of 0, endoscopic remission is defined as an MES of ≤ 1 , and histologic remission is defined as a Geboes score of < 2 .^{14,15} Patients receive treatment escalation until the achievement of their assigned treatment target.

Treatment algorithms

Treatment algorithms that feature the early use of vedolizumab are followed. A key premise is that the favourable safety profile of vedolizumab allows for its safe and effective use to treat patients who are in symptomatic remission but who have not attained endoscopic or histologic remission. Dose escalation of vedolizumab has been shown to help capture response in long-term and real-world studies.^{16,17} Patients are allocated to treatment algorithms according to their existing UC treatment regimen at screening (figures 2-4). Patients who are naïve to treatment at study entry (algorithm A; figure 2) initially receive a standard first-line therapy regimen comprising an oral 5-aminosalicylate (5-ASA) and/or immunosuppressive agent (ie, azathioprine, 6-mercaptopurine or methotrexate) in combination with an optional oral corticosteroid. Those receiving a non-biologic at study entry start intravenous vedolizumab therapy (algorithm B; figure 3), and those receiving a tumour necrosis

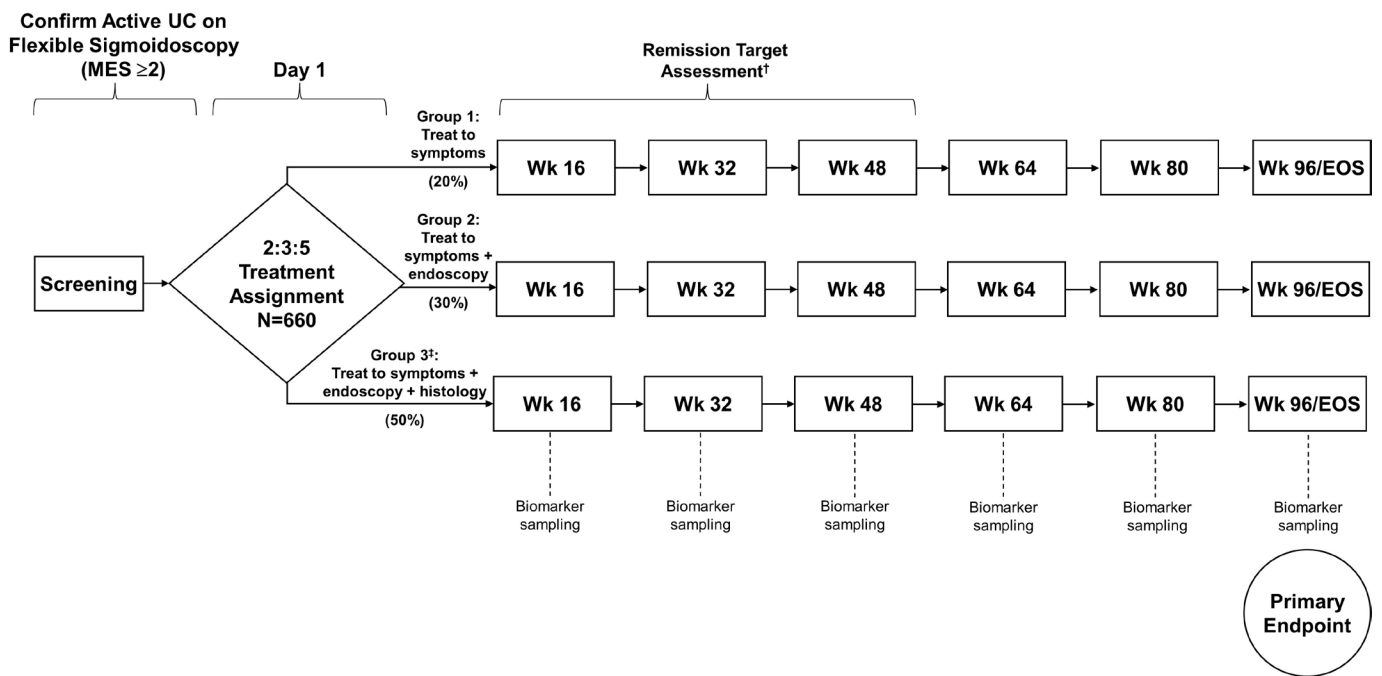


Figure 1 Study schematic. †Periodic interim analyses to check allocation ratio and sample size based on achievement of target. ‡Futility analysis for group 3 as of 1 March 2023 conducted. EOS, end of study; MES, Mayo endoscopic subscore; UC, ulcerative colitis.

factor (TNF) α antagonist, tofacitinib or ustekinumab at study entry are switched to intravenous vedolizumab therapy (algorithm C; figure 4). Appropriate wash-out periods between biologic therapies were determined by the investigators according to their routine clinical practice. Treatment target achievement is assessed at weeks 16, 32 and 48 (figure 1). Corticosteroid-free is defined as not receiving oral corticosteroids at the time of treatment target assessment; any oral corticosteroids initiated at week 32 must be completely tapered at least 4 weeks before the week 48 assessment. Patients who achieve their assigned corticosteroid-free treatment target continue receiving the same treatment regimen. For patients who do not achieve their assigned treatment target due to the use of corticosteroids, these agents are tapered (see Concomitant therapies section for tapering regimen), and the remaining treatment regimen continues from week 16 or escalates from week 32. For patients who do not achieve their assigned treatment target due to a lack of remission (with or without corticosteroid use), therapy is escalated using vedolizumab to a maximum of 300 mg every 4 weeks according to the allocated algorithm. After week 48 and at the investigator's discretion, patients who achieve their treatment target while receiving intravenous vedolizumab every 8 weeks may switch to subcutaneous (SC) vedolizumab administered every 2 weeks, and patients who do not achieve their treatment target may be switched to a non-vedolizumab therapy. Investigators are asked about their adherence to the applicable algorithm and are to document the reason for any non-adherence.

Randomisation and blinding

Eligible patients are randomised in a 2:3:5 ratio to treatment target group 1, 2 or 3. Randomisation is stratified by the following factors: current corticosteroid use (yes; no), current immunosuppressive use (yes; no) and TNF α antagonist use (current; past; never). The goal is for 100 patients in each arm to achieve their treatment target after 48 weeks, with the prespecified possibility to adapt the randomisation ratio in order to achieve this goal (see Interim analyses section). Study site personnel use an interactive web response system for the management of the randomisation procedure and the assignment of each patient to a treatment target group as the patient qualifies for the study.

Patients are blinded to target group assignment, whereas investigators are unblinded. Investigators and site personnel are instructed to neither share patient target group assignments nor influence patient-reported symptom scores. Central readers perform endoscopic and histologic assessments while blinded to treatment target assignments. All endoscopy and histopathology results, along with corticosteroid use and study visit details, are provided to an unblinded offsite assessor. This information is used to inform the site investigator regarding the need to escalate the algorithm. For group 1 (symptomatic remission target), decisions are based on the patient's self-reported symptoms of bleeding and on corticosteroid use. The need to adjust treatment is communicated to patients after 1–3 weeks from the week 16, 32 and 48 study visits to maintain blinding.

For patients who are not on UC treatment at screening, or have only used topical therapy, use the following algorithm:

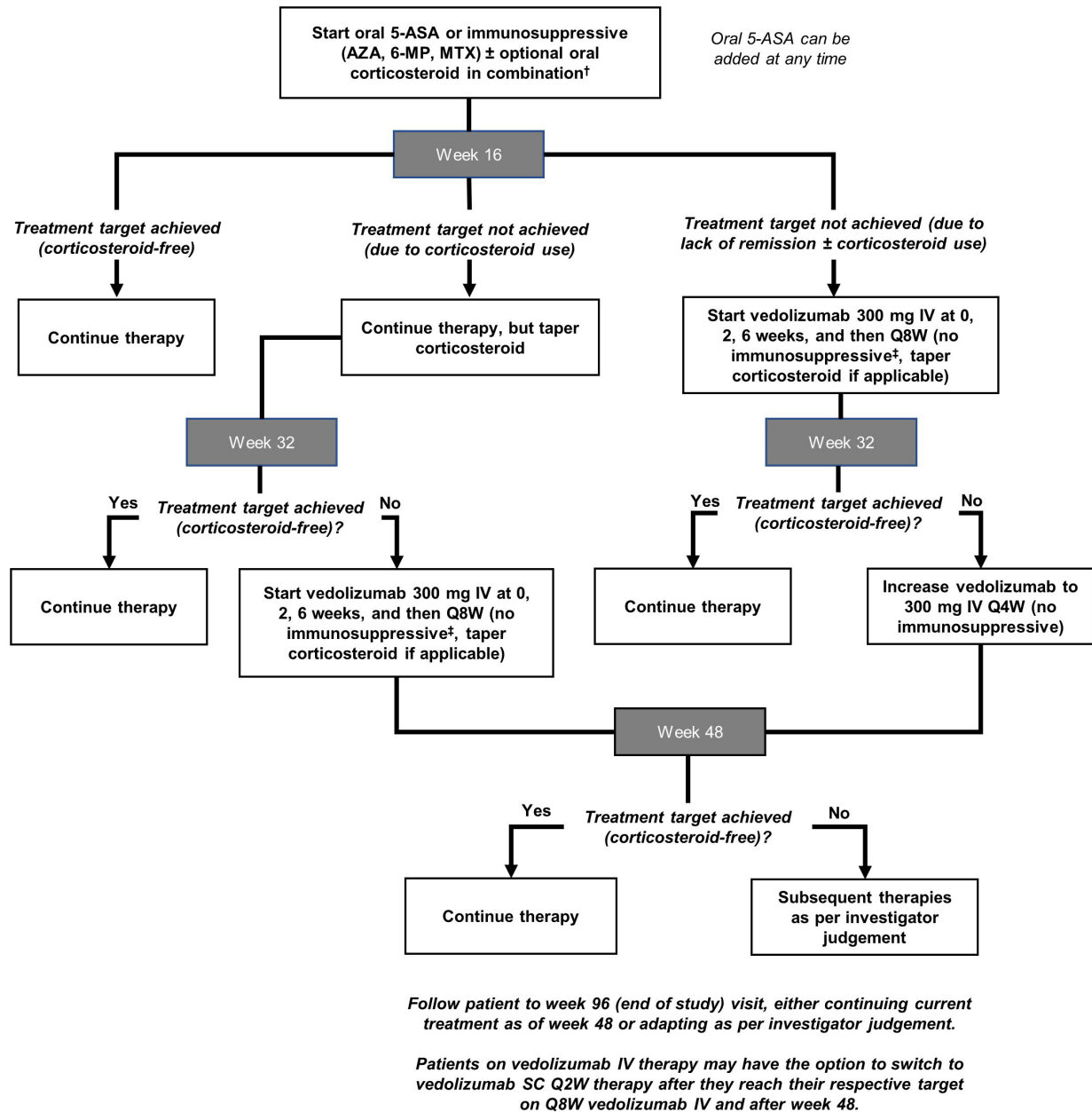


Figure 2 Treatment algorithm A for patients who were treatment naïve at study entry. †If patient uses oral corticosteroid in step 1 of algorithm, taper by week 8. ‡Immunosuppressive treatment must be stopped before starting vedolizumab. 5-ASA, 5-aminosalicylate; 6-MP, 6-mercaptopurine; AZA, azathioprine; IV, intravenous; MTX, methotrexate; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

Assessments

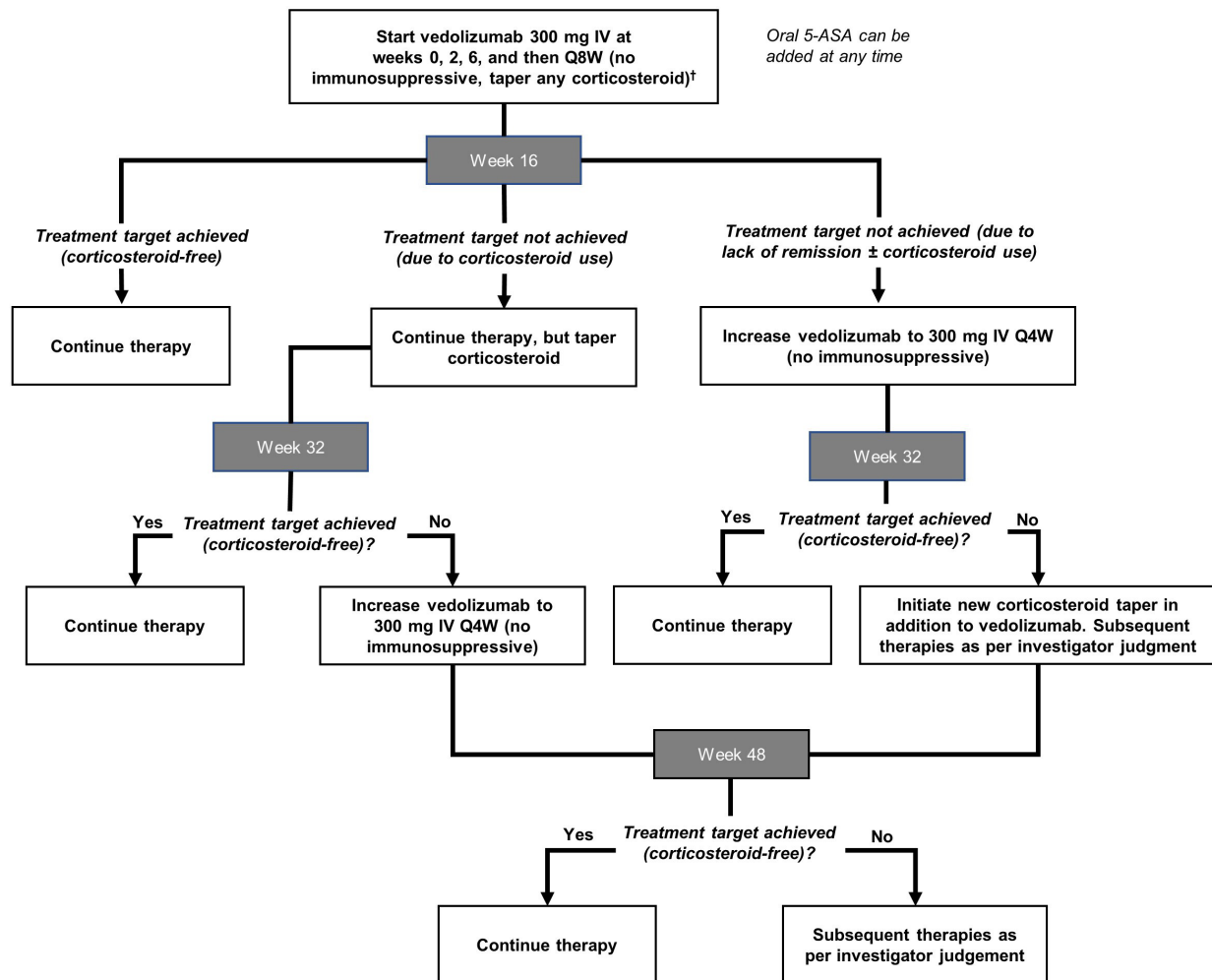
Patients are followed up every 16 weeks of treatment to determine whether their assigned treatment target has been achieved. At weeks 16, 32 and 48, symptoms, endoscopic disease activity, histologic disease activity and corticosteroid use are assessed, and urine, stool, colonic mucosa and blood samples are collected to assess biomarker and drug concentrations. The schedule of enrolment and other assessments is shown in online supplemental table 1.

Study treatment

Study drug

Vedolizumab is central to each treatment algorithm based on its favourable safety profile and effectiveness for patients in symptomatic remission but who have not yet attained endoscopic or histologic remission.¹⁸ All intravenous vedolizumab is provided to sites in 20 mL single-use glass vials, each containing 300 mg of the drug and labelled as ‘investigational product’ in accordance with local regulations. The intravenous infusions are

For patients who are taking 5-ASA (oral), corticosteroid (oral), azathioprine, AZA, 6-MP or MTX at screening, use the following algorithm:



Follow patient to week 96 (end of study) visit, either continuing current treatment as of week 48 or adapting as per investigator judgement.

Patients on vedolizumab IV therapy may have the option to switch to vedolizumab SC Q2W therapy after they reach their respective target on Q8W vedolizumab IV and after week 48.

Figure 3 Treatment algorithm B for patients receiving non-biologic therapies at study entry. †For patients on existing immunosuppressive therapy at randomisation, treatment must be stopped before starting vedolizumab. For patients on existing oral corticosteroid therapy at randomisation, taper by week 8. 5-ASA, 5-aminosalicylate; 6-MP, 6-mercaptopurine; IV, intravenous; MTX, methotrexate; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

administered over the course of approximately 30 min or up to 60 min if required. In an open-label fashion, any SC vedolizumab is provided in single-use bare glass prefilled syringes, each housed in an autoinjector and containing 108mg of the drug. Patients are given reminders at weeks 16, 32, 48, 64 and 80 to adhere to their prescribed treatment(s).

Concomitant therapies

Concomitant oral 5-ASAs or any other non-vedolizumab medications for UC and non-UC indications are permitted at any time during the study. However, stable doses of antidiarrheal therapy and avoidance of topical corticosteroids and 5-ASAs are recommended, with treatment

decisions ultimately at the discretion of the investigator. Oral corticosteroid doses that are stable at randomisation (maximum dose, 30 mg/day prednisone or equivalent) are tapered completely by week 8, if possible, or by week 16 if a slower taper is required. Oral corticosteroids that are initiated at week 32 in algorithms B or C are tapered completely at least 4 weeks before the week 48 assessment to allow for corticosteroid-free treatment target achievement at week 48. The corticosteroids may be held, increased or reinitiated at the discretion of the treating physician up to the dose at randomisation or 30 mg/day of prednisone or equivalent (whichever is lower) for patients who do not tolerate the tapering without clinical

For patients who are taking anti-TNF (infliximab, golimumab, or adalimumab), tofacitinib, or ustekinumab at screening, use the following algorithm:

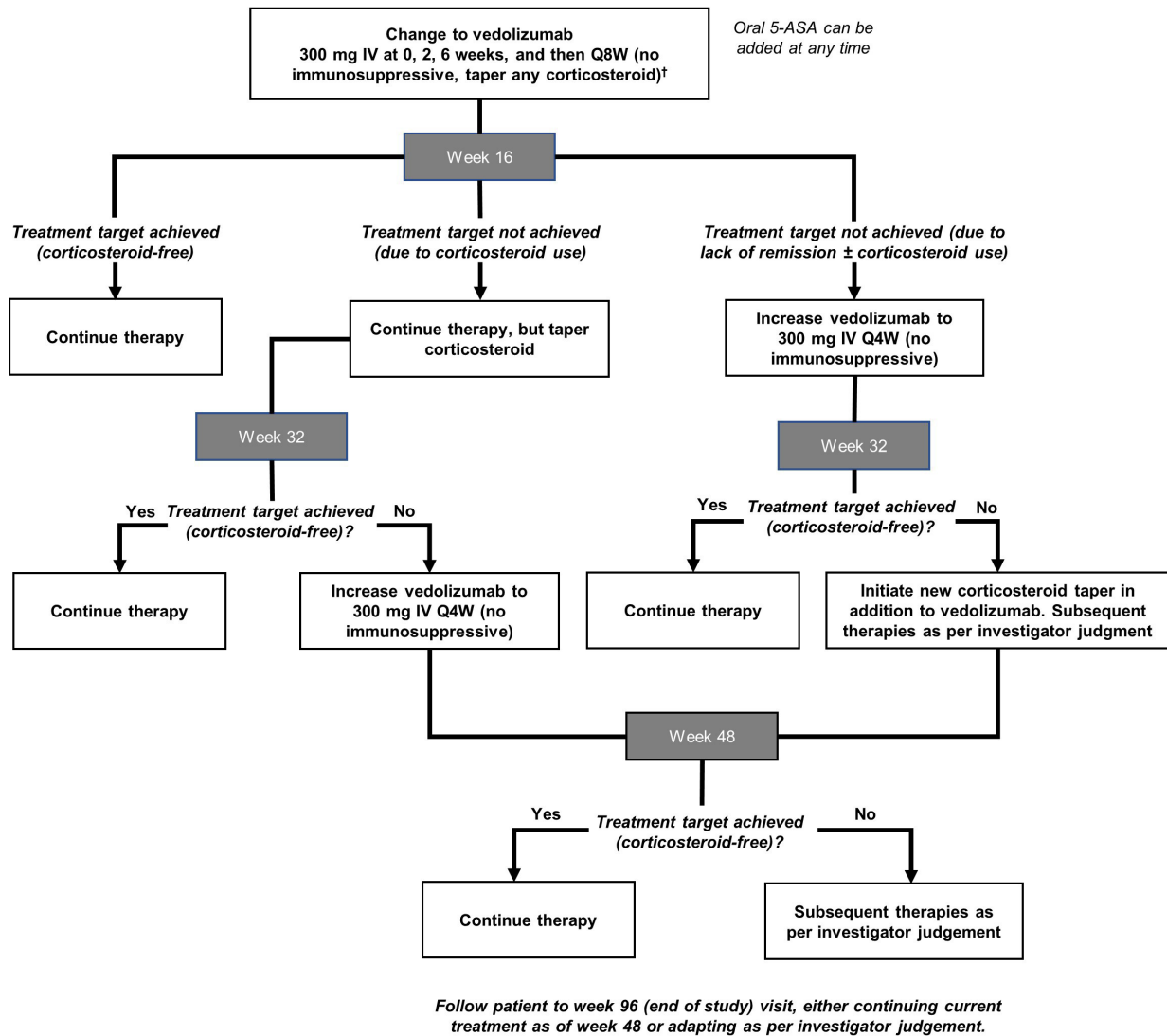


Figure 4 Treatment algorithm C for patients receiving tumour necrosis factor α antagonist, tofacitinib or ustekinumab therapies at study entry. †For patients on existing immunosuppressive therapy at randomisation, treatment must be stopped. For patients on existing oral corticosteroid therapy at randomisation, taper by week 8. 5-ASA, 5-aminosalicylate; IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNF, tumour necrosis factor.

symptom recurrence, but a complete corticosteroid taper is required to fully achieve the treatment targets.

Patient eligibility

Patients who meet all inclusion criteria and do not exhibit any of the exclusion criteria may be enrolled in the study (box 1).

Study objectives and outcomes

The specific objectives and outcomes of this trial are shown in table 1. The primary outcome and several secondary outcomes involve evaluation of the time to a UC-related complication, defined as any of the following complications: (1) hospitalisation for treatment of a UC flare; (2) colectomy for UC (ie, chronic active or acute

severe colitis, but not primarily for dysplasia); (3) rescue therapy use for a UC flare (eg, initiation or dose intensification of a corticosteroid, TNF α antagonist, vedolizumab, tofacitinib or ustekinumab); (4) UC treatment-related complication or (5) other UC-related complication. All cases deemed by the site investigator to have met any component of the UC-related complication definition will be adjudicated by an independent, blinded adjudication panel.

Primary objective and efficacy outcome

The primary objective is to determine whether a treatment target of corticosteroid-free symptomatic+endoscopic+histologic remission is superior to a treatment

Box 1 Inclusion and exclusion criteria for the VERDICT trial
Inclusion criteria

1. Age ≥ 18 years.
2. Diagnosis of UC confirmed by clinical, endoscopic and histologic evidence prior to screening as per standard criteria.
3. Moderately to severely active UC with a Mayo rectal bleeding subscore ≥ 1 and a MES ≥ 2 , with minimum disease extent of 15 cm and objective evidence of inflammation that can be visualised using central endoscopic imaging system.
4. Ability of patient to participate fully in all aspects of this clinical trial.
5. Written informed consent must be obtained and documented.
6. Agree not to participate in an investigational trial for the duration of the trial (observation or other non-interventional trials may be permitted at the discretion of the investigator).
7. Negative standard of care TB test and hepatitis B and C test prior to randomisation unless negative results available from within 12 months prior.
8. A male patient who is non-sterilised and sexually active with a female partner of childbearing potential agrees to use adequate contraception from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.
9. A female patient of childbearing potential who is sexually active with a non-sterilised male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.
10. Up to date with colorectal carcinoma surveillance according to local standards and guidelines. If a patient is not up to date at screening, a standard of care surveillance assessment may be performed during the screening period.
11. Patients who are not responding to their existing treatment for UC.*

Exclusion criteria

1. Patients who have historically failed (ie, had an inadequate response with, lost response to or were intolerant to) 2 or more compounds or classes of advanced therapeutic options (biologics or small molecules; eg, anti-TNF α s, ustekinumab or tofacitinib) for the treatment of their UC.
2. Current or previous treatment with vedolizumab, etrolizumab or natalizumab.
3. Topical therapy (corticosteroid or 5-ASA) use within 2 weeks prior to screening endoscopy.
4. Change to oral corticosteroid dosing within 2 weeks prior to randomisation or a corticosteroid dose of >30 mg/day of prednisone or equivalent at randomisation.
5. Known diagnosis of CD, indeterminate colitis, ischaemic colitis, radiation colitis, diverticular disease associated with colitis or microscopic colitis.
6. Short gut syndrome.
7. Positive stool culture for or active *Clostridioides difficile* infection (as demonstrated by positive toxin and/or antigen).
8. Known hepatitis B or C infection. If a negative test result is available in the 12 months prior to randomisation, retesting is not required.
9. Known active or latent TB; if a negative test result is available in the 12 months prior to randomisation, confirmatory testing (per standard of care) is not required before randomisation.
10. Received any investigational drug within 30 days prior to randomisation/target assignment.

Continued

Box 1 Continued

11. Serious underlying disease other than UC that in the opinion of the investigator may interfere with the patient's ability to participate fully in the study or would compromise patient safety (such as history of malignancies, major neurological disorders or any unstable or uncontrolled medical disorder).
12. History of alcohol or drug abuse that in the opinion of the investigator may interfere with the patient's ability to comply with the study procedures.
13. The patient has active cerebral/meningeal disease, signs, symptoms or any history of PML prior to randomisation.
14. Hypersensitivity to any excipient of vedolizumab.
15. Active severe infection such as sepsis, cytomegalovirus, listeriosis or opportunistic infection.
16. History of HIV or positive test at screening (Italy-specific criterion).
17. Any other contraindication(s) to vedolizumab (Italy-specific criterion).
18. If female, the patient is pregnant or lactating or intending to become pregnant before, during or within 18 weeks after the last dose; or intending to donate ova during such time period.
19. If male, the patient intends to donate sperm during the course of this study or for 18 weeks after the last dose.
20. Vaccination with a live or live-attenuated vaccine within 4 weeks prior to randomisation, or planned vaccination during conduct of the study, except vaccination for COVID-19.

*According to the investigators' discretion, consistent with a standard of care-based protocol; a minimum duration of treatment/non-response was not defined.
5-ASA, 5-aminosalicylate; CD, Crohn's disease; MES, Mayo endoscopic score; PML, progressive multifocal leukoencephalopathy; TB, tuberculosis; TNF, tumour necrosis factor; UC, ulcerative colitis; VERDICT, active ulcerative colitis, a Randomised Controlled Trial.

target of corticosteroid-free symptomatic remission alone, with regard to the primary efficacy outcome within up to 80 weeks of follow-up after target achievement. The primary efficacy outcome is the time from treatment target achievement to a UC-related complication among patients who achieved their assigned treatment target. For the primary analysis, this outcome will be compared between treatment target group 1 (corticosteroid-free symptomatic remission) and treatment target group 3 (corticosteroid-free symptomatic, endoscopic and histologic remission).

Secondary objectives and efficacy outcomes

Secondary objectives include those comparing the time to a UC-related complication among different subgroups and treatment target groups, those assessing the time to treatment target achievement and to each specific UC-related complication (eg, hospitalisation), and those measuring safety and changes in various biomarkers and indices of disease activity and quality of life. The secondary objectives and efficacy outcomes are described in detail in [table 1](#).

Safety outcomes

All adverse events (AEs), serious AEs (SAEs), significant clinical laboratory abnormalities and changes in vital

Table 1 Specific objectives and outcome measures of the VERDICT trial

Primary objective	Primary outcome measure	Population(s)
To determine whether a treatment target of corticosteroid-free symptomatic, endoscopic and histologic remission (group 3) is superior to corticosteroid-free symptomatic remission (group 1)	Time from treatment target achievement to a UC-related complication*	Achieved-target population†
Secondary objectives	Secondary outcome measures	Population(s)
1. To evaluate time to a UC-related complication in all randomised patients including subgroups on and off corticosteroids at the time of achieving other relevant components of the treatment target	Time from treatment target achievement to a UC-related complication*	All randomised patients
2. To determine whether a treatment target of corticosteroid-free symptomatic and endoscopic remission (group 2) is superior to corticosteroid-free symptomatic remission (group 1)	Time from treatment target achievement to a UC-related complication*	All randomised patients, achieved-target population†
3. To determine whether a treatment target of corticosteroid-free symptomatic, endoscopic and histologic remission (group 3) is superior to corticosteroid-free symptomatic and endoscopic remission (group 2)	Time from treatment target achievement to a UC-related complication*	All randomised patients, achieved-target population†
4. To evaluate the time to a UC-related complication in the subgroup of patients who exclusively achieve their treatment target and not a higher target by week 48	Time from treatment target achievement to a UC-related complication*	Achieved-target population†
5. To assess the time to achieve the respective treatment targets among the randomised groups‡	Time to treatment target achievement	Achieved-target population†
6. To evaluate the time to each type of UC-related complication across the treatment target groups	Time to hospitalisation, colectomy, rescue therapy, treatment-related and other UC-related complications	All randomised patients, achieved-target population†
7. To assess the effect of treatment(s) on UC-related complications that is mediated through treatment targets	Total treatment effects partitioned into direct and indirect effects	Achieved-target population†
8. To evaluate the change in FC levels from baseline	Change in FC levels from baseline to all follow-up visits	All randomised patients, achieved-target population†
9. To evaluate the change in CRP concentrations from baseline	Change in CRP concentrations from baseline to all follow-up visits	All randomised patients, achieved-target population†
10. To evaluate the change in UC-100 score from baseline	Change in UC-100 score from baseline to weeks 16, 32, 48 and 96	All randomised patients, achieved-target population†
11. To evaluate changes in HRQoL from baseline	Change in IBDQ from baseline to all follow-up visits	All randomised patients, achieved-target population†
12. To evaluate changes in the WPAI-UC questionnaire from baseline	Change in the WPAI-UC questionnaire from baseline to all follow-up visits	All randomised patients, achieved-target population†
13. To evaluate changes in MCS including the MES and other subcomponents from baseline	Change in MCS, MES and other MCS subcomponents from baseline to weeks 16, 32, 48 and 96	All randomised patients, achieved-target population†
14. To describe changes in the Geboes score from baseline	Change in Geboes score from baseline to weeks 16, 32, 48 and 96	All randomised patients, achieved-target population†
15. To describe changes in the RHI score from baseline	Change in RHI score from baseline to weeks 16, 32, 48 and 96	All randomised patients, achieved-target population†
16. To describe changes in the Nancy Histological Index from baseline	Change in Nancy Histological Index score from baseline to weeks 16, 32, 48 and 96	All randomised patients, achieved-target population†
17. To evaluate the number of AEs and SAEs among the three randomised groups	AE and SAE counts	All randomised patients

Continued

**Table 1** Continued

Secondary objectives	Secondary outcome measures	Population(s)
18. To explore urine, stool, colonic mucosa and serum samples for biomarkers and drug concentrations that are associated with clinically important outcomes	Change in biomarkers and drug concentrations from baseline to all time points; association between biomarkers and drug concentrations	All randomised patients
19. To validate the SIQ-UC tool in English-fluent patients	Correlations with the SIQ-UC for the IBDQ, WPAI-UC, PGIS and PGIC; the ability of the SIQ-UC to distinguish between patients by PGIS and PGIC disease severity	All randomised patients

*Defined as any of the following: (1) hospitalisation for treatment of a UC flare; (2) a colectomy for UC (defined as a colectomy for chronic active or acute severe colitis, but not primarily for dysplasia); (3) rescue therapy (such as new initiation or dose intensification of a corticosteroid, TNF α antagonist, vedolizumab, tofacitinib or ustekinumab) for a documented UC flare; (4) a UC treatment-related complication or (5) other disease-related complication.

†Defined as all randomised patients who achieved their assigned treatment target.

‡Time will be censored for patients who do not achieve their assigned target by week 48.

AE, adverse event; CRP, C reactive protein; EOS, end of study; FC, faecal calprotectin; HRQoL, health-related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Score; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; RHI, Roberts Histopathology Index; SAE, serious adverse event; SAP, statistical analysis plan; SIQ-UC, Symptoms and Impacts Questionnaire for UC; TNF, tumour necrosis factor; UC, ulcerative colitis; VERDICT, active ulcerative colitis, a Randomised Controlled Trial; WPAI-UC, Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis.

signs are being reported for all groups from screening to the end of the study among all randomised patients. The AE and SAE counts for each group are evaluated as a secondary outcome (table 1).

Exiting the study

Patients will be discontinued from the study after meeting the primary outcome (ie, a UC-related complication), experiencing an AE that imposes unacceptable risk, deviating from the protocol, being lost to follow-up or after making the decision to withdraw.

Data collection, monitoring and management

Study data are being collected and entered into a web-based electronic case report form software solution within five business days of each study visit, and data validation edit checks will be implemented.

Statistical analyses

Primary analyses

The primary efficacy analyses will be based on the achieved-target analysis set, defined as all randomised patients who achieved their assigned treatment target, using the time from target achievement to a UC-related complication as the outcome. The primary efficacy evaluation is to compare the time to a UC-related complication between treatment target groups 1 and 3 among those who initially achieve their target. If this comparison results in a two-sided $p < 0.05$, then the time to a UC-related complication will also be compared between treatment target groups 1 and 2. Time will be censored for patients who are lost to follow-up or who do not experience a UC-related complication by the end of the study. Between-group comparisons will be conducted using the Cox proportional hazard model with time-dependent covariates to account for different treatment target

achievement times among different groups. The analysis will also adjust for prognostic factors used in the stratification process and for treatment received by drug class, and frailty models will be used to adjust for potential centre heterogeneity.

Secondary analyses

The secondary analyses will be based on the full analysis set, defined as all randomised patients and/or the achieved-target analysis set (table 1). The time-to-event secondary outcomes (secondary outcomes 1–6) will be assessed using the Cox proportional hazard model with adjustment for the prognostic factors used for group allocation. For all time-to-event outcomes, adjusted HRs, associated 95% CIs and two-sided p values will be calculated to quantify the magnitude of the differences, and no imputation of missing data will be performed.

Additional prespecified statistical approaches will be used for the remaining secondary outcomes. Mediation analysis for secondary outcome 7 will be performed by partitioning total effects into direct and indirect effects,¹⁹ and secondary outcomes 8–16 will be analysed using a likelihood-based linear mixed effects model for repeated measures with covariate adjustment for baseline scores and prognostic factors used for group allocation. Appropriate contrasts from mixed models will be used for between-group comparisons at specific follow-up times. As this approach is based on likelihoods, which is valid under the assumption of data missing at random, multiple imputations will not be conducted. Secondary outcome 17 (ie, AE count data) will be analysed for the full analysis set using appropriate statistical methods for counts and presented using descriptive statistics. For secondary outcome 18, the change from baseline in biomarkers from urine, stool, colonic mucosa and blood samples

by time point will be the dependent variable; time, drug and interaction between drug treatment and time will be included as fixed effects; and patients will be included as a random effect. A linear mixed-model will then be used to evaluate the association between biomarkers and drug concentrations, which will be performed using a random effect on both intercept and slope, allowing each patient to have his or her own drug concentration–biomarker relationship. Two-sided values of $p < 0.05$ will be considered statistically significant without adjustment for multiplicity and should be interpreted with caution.

To validate the Symptoms and Impacts Questionnaire for UC (SIQ-UC) tool in English-fluent patients (secondary outcome 19), correlations between the SIQ-UC and the Inflammatory Bowel Disease Questionnaire, Work Productivity and Activity Impairment Questionnaire: UC, Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) will be assessed using Spearman's correlation coefficients. The known-groups validity will be examined to determine whether the SIQ-UC can distinguish between patients by disease severity, as defined by the PGIS and PGIC. Analysis of covariance models with baseline clinical measurement group as the main effect will be used, adjusting for age and gender.

Interim analyses

A prespecified interim analysis of the proportion of patients who achieve their assigned treatment targets was performed once 50 patients in each treatment target group reached the 16-week assessment. Findings from periodic analyses throughout the target achievement phase are used to check assumptions regarding treatment target achievement to allow for sample size re-estimation if required or adaptation of the randomisation ratio. These interim analyses are conducted and reviewed by a statistician, epidemiologist and clinician who have no contact with patients in the study.

Stopping rule for futility

The proportion of patients in group 3 who achieved corticosteroid-free clinical+endoscopic+histologic remission as of 1 March 2023 was estimated with a 95% CI in a futility analysis. If the targeted rate of 30% was above the upper bound of the 95% CI, group 3 was to be stopped on the grounds of futility.

Sample size

The design of this trial was based on 48-week treatment target achievement estimates of 80% for group 1, 50% for group 2 and 30% for group 3. The random assignment of 660 patients in a 2:3:5 ratio would lead to 132:198:330 patients in each arm, respectively, and an estimated 100 patients in each arm who achieve their respective treatment target. The UC-related complication rate estimates of 23% for group 1 and 7% for group 3 were based on relapse rates reported at week 52 in a prospective study of 179 patients with UC in clinical remission at baseline

(relapse rate, 23%), of whom 82 patients were in clinical, endoscopic and histologic remission at baseline (relapse rate, 7%).⁷ Using the two-sample log-rank test, the primary comparison between groups 1 and 3 (with 100 patients in each arm who achieve their respective target) will have 95% power to detect the difference at the 2-sided 5% significance level. This calculation assumes that the study duration comprises 32 weeks for patients to achieve their respective target (from weeks 16 to 48) and 48 weeks of additional follow-up. A separate statistical analysis plan will be developed prior to database lock.

STUDY PROGRESS AND INTERIM ANALYSIS

Demographics

The VERDICT study was initiated in September 2020. As of 1 March 2023, 432 patients (89, 130, and 213 patients for groups 1, 2 and 3, respectively) were enrolled and randomised at 50 sites across 10 North American and European countries. Mean (SD) baseline characteristics (table 2) include a UC duration of 8.1 (8.2) years, Mayo Clinic score of 8.6 (1.7), C reactive protein level of 13.4 (16.1) mg/L and a faecal calprotectin level of 1495.6 (1489.3) mg/kg. At baseline, 52% (224/432) and 10% (44/432) of patients were receiving concomitant corticosteroids and immunosuppressives, respectively, and 14% (62/432) of patients had current or prior exposure to TNF α antagonists. Most patients (86%) were receiving non-biologic therapy. Enrolment of bionative patients was capped in May 2023, aiming for bio-exposed patients to comprise approximately 30% of the total study population. This change was approved by the trial steering committee on the review of interim baseline trial results indicating that the population comprised primarily bionative patients.

Futility analysis

In all randomised patients, regardless of how far they were in the trial as of 1 March 2023, 51% (95% CI: 40% to 61%), 37% (95% CI: 29% to 46%), and 33% (95% CI: 27% to 40%) of patients in groups 1, 2 and 3, respectively, had achieved their assigned treatment target (table 3, online supplemental figure 1). The upper bound of the 95% CI for group 3 target achievement is above the targeted rate of 30%, thus meeting the criteria to continue group 3. Of the patients who reached at least the 16-week visit, 75% (95% CI: 62% to 85%), 52% (95% CI: 41% to 62%) and 49% (95% CI: 40% to 57%) of patients in groups 1, 2 and 3, respectively, achieved their assigned treatment target.

Randomisation ratio

As described in the study protocol, the randomisation of 660 patients in a ratio of 2:3:5 would result in 132:198:330 patients in groups 1, 2 and 3, respectively. The protocol also indicates an estimate of 100 randomised patients per group who will achieve the respective target. Currently, of the 432 randomised patients (89, 130 and 213 for groups 1, 2 and 3, respectively; online supplemental figure 1), 164 patients have achieved their assigned treatment

Table 2 Demographics and baseline characteristics

Characteristic	Treatment target groups*			
	Group 1 (N=89)	Group 2 (N=130)	Group 3 (N=213)	Total (N=432)
Male, n (%)	51 (57.3)	67 (51.5)	122 (57.3)	240 (55.6)
Age (years), mean (SD)	42.8 (14.9)	41.5 (15.3)	40.8 (14.1)	41.4 (14.6)
Race, n (%)				
Asian	9 (10.1)	8 (6.2)	9 (4.2)	26 (6.0)
Black or African American	2 (2.2)	4 (3.1)	7 (3.3)	13 (3.0)
White	75 (84.3)	114 (87.7)	186 (87.3)	375 (86.8)
Other/unknown	3 (3.4)	4 (3.1)	11 (5.2)	18 (4.2)
Height (cm), mean (SD)	170.9 (9.0)	171.2 (10.4)	172.8 (9.1)	171.9 (9.5)
Weight (kg), mean (SD)	77.1 (18.9)	75.8 (15.6)	76.8 (16.4)	76.6 (16.6)
BMI (kg/m ²), mean (SD)	26.4 (6.4)	25.8 (5.1)	25.6 (4.7)	25.8 (5.2)
Mayo Clinic score, mean (SD)	8.6 (1.6)	8.6 (1.8)	8.7 (1.7)	8.6 (1.7)
Mayo endoscopic score (MES), mean (SD)	2.6 (0.5)	2.6 (0.5)	2.6 (0.5)	2.6 (0.5)
Partial Mayo Clinic score, mean (SD)	6.0 (1.4)	6.0 (1.6)	6.1 (1.6)	6.0 (1.5)
IBDQ score, mean (SD)	126.7 (34.6)	131.8 (34.6)	128.2 (36.1)	129.0 (35.3)
Disease duration (y), mean (SD)	8.0 (8.2)	8.2 (8.9)	8.1 (7.8)	8.1 (8.2)
Disease severity, n (%)				
Mild	6 (6.7)	7 (5.4)	10 (4.7)	23 (5.3)
Moderate	57 (64.0)	91 (70.0)	120 (56.3)	268 (62.0)
Severe	11 (12.4)	7 (5.4)	32 (15.0)	50 (11.6)
Missing	15 (16.9)	25 (19.2)	51 (23.9)	91 (21.1)
CRP (mg/L), mean (SD)	9.9 (7.6)	12.9 (18.4)	15.0 (17.0)	13.4 (16.1)
FC (mg/kg), mean (SD)	1667.0 (1646.1)	1380.2 (1400.8)	1494.5 (1494.5)	1495.6 (1489.3)
Albumin (g/dL), mean (SD)	44.6 (4.2)	44.4 (4.1)	44.1 (3.7)	44.3 (3.9)
Haematocrit (%), mean (SD)	0.43 (0.06)	0.42 (0.05)	0.43 (0.05)	0.43 (0.05)
Haemoglobin (g/dL), mean (SD)	134.2 (19.4)	129.1 (20.0)	133.6 (18.4)	132.4 (19.2)
Leucocytes (10 ⁹ /L), mean (SD)	7.7 (2.9)	8.1 (2.8)	8.0 (3.2)	8.0 (3.0)
Current CS use, n (%)	45 (50.6)	68 (52.3)	111 (52.1)	224 (51.9)
Current IS use, n (%)	10 (11.2)	13 (10.0)	21 (9.9)	44 (10.2)
Current anti-TNF α use, n (%)	3 (3.4)	2 (1.5)	5 (2.3)	10 (2.3)
Previous anti-TNF α use, n (%)	11 (12.4)	17 (13.1)	24 (11.3)	52 (12.0)
Previous medication use, [†] n (%)	77 (86.5)	116 (89.2)	184 (86.4)	377 (87.3)

*Group 1: CS-free symptomatic remission (Mayo RBS=0); group 2: CS-free endoscopic remission (MES \leq 1)+symptomatic remission; group 3: CS-free histologic remission (Geboes score<2B.0)+endoscopic remission+symptomatic remission.

[†]Previous medications included topical agents for haemorrhoids and anal fissure treatment, anticestodals, antidiarrhoeal micro-organisms, antiemetics and antinauseants, antigout preparations, antimetabolites, blood and related products, calcium, systemic corticosteroids, drugs for constipation, drugs for functional gastrointestinal disorders, drugs for peptic ulcer and gastro-oesophageal reflux disease, drugs for treatment of tuberculosis, immunostimulants, immunosuppressants, intestinal anti-infectives, intestinal anti-inflammatory agents, iron preparations, opioids, other analgesics and antipyretics, quinolone and other antibacterials, stromatological preparation, unspecified herbal and traditional medicine, viral vaccines and vitamin B₁₂ and folic acid.

BMI, body mass index; CRP, C reactive protein; CS, corticosteroid; FC, faecal calprotectin; IBDQ, Inflammatory Bowel Disease Questionnaire; IS, immunosuppressive; RBS, rectal bleeding subscore; TNF, tumour necrosis factor.

target (45, 48 and 71 for groups 1, 2 and 3, respectively), representing a target achievement rate of 38% on average across the three groups. However, this rate is underestimated because it does not account for the 167 patients who are still ongoing in the study (27, 52 and 88 for groups 1, 2 and 3, respectively). Accounting for both these patients and dropouts, calculations projected that 62 patients (70%), 77 patients (59%) and 110 patients (52%) in groups 1, 2 and 3, respectively, will achieve

their treatment target by week 48 (online supplemental methods and figure 2).

Based on the initial design to randomise 660 patients in a 2:3:5 ratio (132, 198 and 330 for groups 1, 2 and 3, respectively), the estimated numbers of patients who will achieve their treatment target at week 48 are 92 (group 1), 117 (group 2) and 172 (group 3). The number of patients who achieve their treatment target would fall short of the planned 100 patients in group 1 and would be higher

Table 3 Treatment target achievement

	Treatment target groups*		
	Group 1 (N=89)	Group 2 (N=130)	Group 3 (N=213)
Week 16†	N=60	N=93	N=146
CS-free remission, n	39	35	56
No remission, n	21	58	90
Week 32†	N=15	N=30	N=62
CS-free remission, n	6	8	10
No remission, n	9	22	52
Week 48†	N=2	N=13	N=24
CS-free remission, n	0	5	5
No remission, n	2	8	19
1 March 2023			
CS-free remission (cumulative), n	45	48	71
CS-free remission among all randomised patients, % (95% CI)	51 (40 to 61)	37 (29 to 46)	33 (27 to 40)
CS-free remission among patients who reached at least week 16, % (95% CI)	75 (62 to 85)	52 (41 to 62)	49 (40 to 57)

*Group 1: CS-free symptomatic remission (Mayo RBS=0); group 2: CS-free endoscopic remission (MES≤1)+symptomatic remission; group 3: CS-free histologic remission (Geboes score<2B.0)+endoscopic remission+symptomatic remission.
†Patients who achieved remission at an earlier time point are not included in the subsequent visit's population.
CS, corticosteroid; MES, Mayo Endoscopic Score; RBS, rectal bleeding subscore.

than the planned 100 patients each in groups 2 and 3. To ensure that each group will meet the goal of 100 patients who achieve their target, the randomisation ratio for the remaining 228 patients (660–432) would require adaptation. Based on the treatment target achievement rates observed in each group to date, an expected minimum of 143 (100/0.7), 170 (100/0.59) and 192 (100/0.52) randomised patients are required for groups 1, 2 and 3, respectively. These numbers correspond to an additional 54 patients needed for group 1 and an additional 40 patients for group 2, while no additional patients are needed for group 3. To maintain the same overall sample size while balancing the target number of patients who achieve their target across the three groups, a revised randomisation ratio of 5:4:1 was implemented on 5 May 2023 for the last 188 patients (228–40, with 40 being the estimated number of additional patients still randomised in the original 2:3:5 ratio). These randomisation ratios for the remaining 228 patients to be randomised correspond to 102 patients in group 1, 87 patients in group 2 and 39 patients in group 3. The revised randomisation ratio will balance the final number of patients achieving their treatment targets across all three groups.

DISCUSSION

The VERDICT trial is underway to determine the optimal treatment target in UC.^{6 7} As of 1 March 2023, 432 patients have been randomised, representing approximately 65% of the target enrolment of 660 patients. The recruitment rate has been on target, and the protocol has otherwise been followed

to date. Consistent with findings from a previous interim analysis,^{10 11} interim results reported here further confirm the continued enrolment of a typical moderate to severe UC population and the feasibility of achieving the treatment targets in each of the three groups. Full study completion and results are expected in 2025. Final results will be published in peer-reviewed journals and presented at scientific meetings. Results of this study will help to inform treatment targets in clinical practice, drug development and future evidence-based guidelines.

Dissemination

Investigators will be responsible for obtaining documented informed consent from all patients prior to study participation. This study is registered in the EudraCT registry (identifier: 2019-002485-12) and the ClinicalTrials.gov registry (identifier: NCT04259138). Results will be disseminated in peer-reviewed journals and at scientific congresses.

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