BMJ Open Gastroenterology

Protocol for a multicentred randomised controlled trial investigating the use of personalised golimumab dosing tailored to inflammatory load in ulcerative colitis: the GOAL-ARC study (GLM dose Optimisation to Adequate Levels to Achieve Response in Colitis) led by the INITIAtive group (NCT 0268772)

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To cite: Sheridan J, Coe CA, Doran P, *et al*. Protocol for a multicentred randomised controlled trial investigating the use of personalised golimumab dosing tailored to inflammatory load in ulcerative colitis: the GOAL-ARC study (GLM dose Optimisation to Adequate Levels to Achieve Response in Colitis) led by the INITIAtive group (NCT 0268772). *BMJ Open Gastro* 2018;**5**:e000174. doi:10.1136/bmjgast-2017-000174

Received 22 August 2017
Revised 12 October 2017
Accepted 17 October 2017

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ABSTRACT

Introduction Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD), often leading to an impaired quality of life in affected patients. Current treatment modalities include antitumour necrosis factor (anti-TNF) monoclonal antibodies (mABs) including infliximab, adalimumab and golimumab (GLM). Several recent retrospective and prospective studies have demonstrated that fixed dosing schedules of anti-TNF agents often fails to consistently achieve adequate circulating therapeutic drug levels (DL) with consequent risk of immunogenicity treatment failure and potential risk of hospitalisation and colectomy in patients with UC. The design of GLM dose Optimisation to Adequate Levels to Achieve Response in Colitis aims to address the impact of dose escalation of GLM immediately following induction and during the subsequent maintenance phase in response to suboptimal DL or persisting inflammatory burden as represented by raised faecal calprotectin (FCP).

Aim The primary aim of the study is to ascertain if monitoring of FCP and DL of GLM to guide dose optimisation (during maintenance) improves rates of patient continuous clinical response and reduces disease activity in UC.

Methods and analysis A randomised, multicentred two-arm trial studying the effect of dose optimisation of GLM based on FCP and DL versus treatment as per SMPC. Eligible patients will be randomised in a 1:1 ratio to 1 of 2 treatment groups and shall be treated over a period of 46 weeks.

Ethics and dissemination The study protocol was approved by the Research Ethics committee of St. Vincent's University Hospital. The results will be published in a peer-reviewed journal and shared with the worldwide medical community.

Trial registration numbers EudraCT number: 2015-004724-62; Clinicaltrials.gov Identifier: NCT0268772; Pre-results.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) condition. Males and females are affected equally and patients can be diagnosed at any age, including babies and children. The peak age of incidence is between the ages of 15 and 35 years, with a second (smaller) peak from the 50s to 70s. Incidence rates are increasing worldwide.[1] Current treatment modalities include 5-aminosalicylates, steroids, immunomodulators such as azathioprine or 6-mercaptopurine, antitumour necrosis factor (anti-TNF) monoclonal antibodies (mABs) including intravenous infliximab (IFX) and subcutaneous forms, adalimumab and golimumab (GLM).

Several recent retrospective and prospective studies have demonstrated that fixed dosing schedules of anti-TNF agents often fails to consistently achieve adequate circulating levels of therapeutic antibody with consequent risk of immunogenicity,

treatment failure and the associated risk of hospitalisation and colectomy in patients with UC.[2 3]

The PURSUIT studies (Programme of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment) have demonstrated the safety and efficacy of GLM for induction and maintenance in moderate to severely active UC. Continuous clinical response (CCR) was achieved in 49.7% (100 mg) and 47% (50 mg), respectively. Analysis of serum GLM concentration at week 54 showed that those patients with levels in the highest quartile (>4.13 µg/mL) had the greater numerical likelihood of achieving CCR (92.3%).[4 5] The authors of PURSUIT state that these findings may be explored further in future clinical trials in which GLM concentrations are measured and GLM is variably dosed to achieve target exposure, compared with fixed dosing regimes. Recently, the TAXIT trial (Trough level Adapted infliXImab Treatment) showed that following dose optimisation of IFX in IBD, continued concentration-based dosing compared with clinical-based dosing was associated with fewer flares during the course of treatment over 1 year.[6] There is a paucity of data regarding the potential benefit in terms of CCR rates of early dose optimisation (postinduction) and continued concentration-based dosing of GLM in response to circulating drug levels.

The design of GLM dose Optimisation to Adequate Levels to Achieve Response in Colitis (GOAL-ARC) aims to address precisely this question by testing the impact of dose escalation of GLM immediately following induction and during the subsequent maintenance phase in response to suboptimal drugs levels or persisting inflammatory burden as represented by raised faecal calprotectin (FCP). FCP has been shown to correlate closely to endoscopic disease activity.[6] High levels have been shown to predict relapse in IBD[7 8] and in post hoc analysis of the PURSUIT studies, week 6 FCP level as well as change of FCP from baseline were significant predictors of CCR.[9]

In the PURSUIT studies, patients had visits every 4 weeks to the study site and CCR was defined as a maintained response at each visit from week 6 though to week 54. In real-life practice, four weekly visits are impractical for the patient and healthcare providers (HCP) alike. In the Mayo scoring system for UC, the stool and rectal bleeding subscores are reported by the patient and thus do not require a visit to the HCP. Scores of a 6-point scale using only the bleeding and stool frequency components have been shown previously to correlate well with the full Mayo score and the partial Mayo score.[10] GOAL-ARC will use a web-based application to capture patient-reported outcomes (PRO), which will include rectal bleeding and stool frequency subscore as well as the short health scale to measure quality of life (QOL). This will enable CCR to be measured in real-life scenarios. The term pCCR will be used to highlight patient-reported continuous clinical response.

GOAL-ARC attempts to answer the question as to whether adoption of novel tailored dosing strategies, which take account of interindividual differences in inflammatory burden and drug kinetics, might achieve pCCR and remission in a greater proportion of patients.

METHODS AND ANALYSIS

Study design

The study is designed as randomised, multicentred two-arm trial studying the effect of dose optimisation of GLM based on FCP and drug levels versus treatment as per SMPC (see figure 1). Eligible patients will be randomised in a 1:1 ratio to one of two treatment groups. Doses of concomitant medications will remain constant except for corticosteroids, which shall be tapered by 5 mg weekly after week 2 until discontinued.

Study population

Trial subjects

Trial subjects will include all patients aged 18 years and over who have a diagnosis of UC and fit the inclusion criteria as outlined below.

Inclusion criteria

Subjects meeting all of the criteria below may be included in the study.

- Patients aged ≥18 years.
- Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
- Established diagnosis of UC and moderate-to-severe disease activity, defined as a Mayo score of 6–12, with an endoscopic subscore ≥2.
- Patients had an inadequate response to, or had failed to tolerate, one or more of the following conventional therapies: oral 5-aminosalicylates, oral corticosteroids, azathioprine (AZA) and/or 6-mercaptopurine (6MP); or corticosteroid dependent (ie, an inability to taper corticosteroids without recurrence of UC symptoms).

Or

- Patients who are secondary non-responders to anti-TNF agents (lost response after induction therapy) or failed to tolerate a prior anti-TNF agent, for example, an infusion reaction.
- Patients who have not responded to vedolizumab.
- Patients concurrently treated with oral 5-aminosalicylates or corticosteroids are to receive a stable dose for at least 2 weeks before baseline, and patients receiving AZA and/or 6MP are to receive a stable dose for at least 4 weeks before baseline. Patients are required to maintain stable doses of their concomitant UC medications during the study except for corticosteroids, which shall be tapered by 5 mg weekly after week 2 until discontinued.
- Female subjects of childbearing potential must be willing to ensure that they or their partner use effective contraception during the study and for 6 months thereafter.

Or

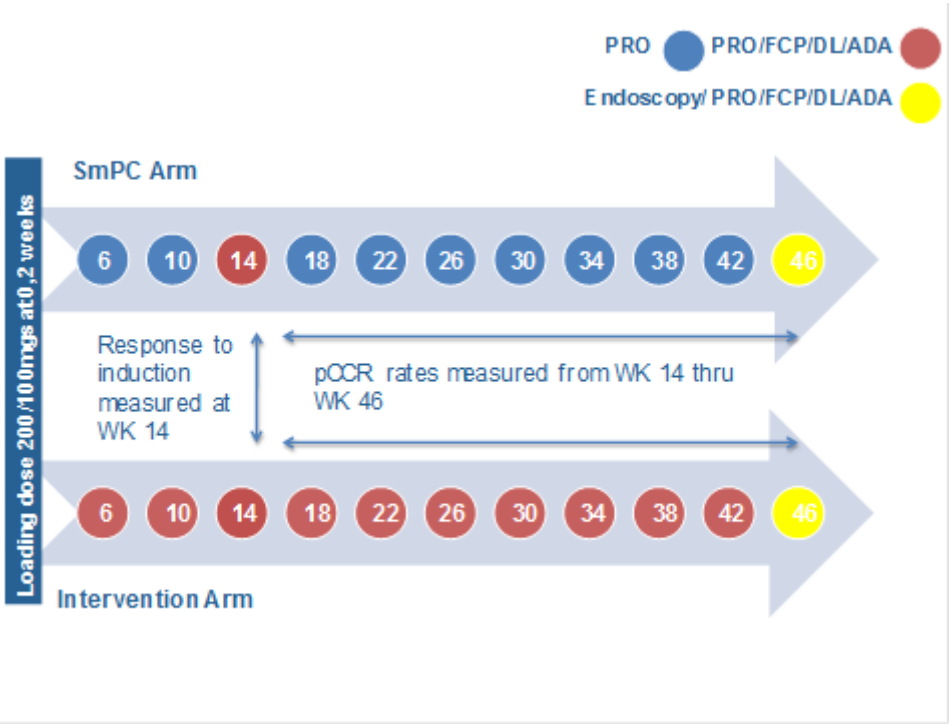

Figure 1 Study Design

ADA, adalimumab; DL, drug levels; FCP, faecal calprotectin; pCCR, patient-reported continuous clinical response; PRO, patient-reported outcomes.

- Surgical sterilised female patients with documentation of prior hysterectomy, tubal ligation or complete bilateral oophorectomy.

Or

- Postmenopausal women with postmenopausal defined as permanent cessation >1 year of previously occurring menses.
- Female subjects' serum or urine pregnancy test performed at the screening visit must be negative.
- Subjects have following investigations within 1 month prior to enrolment (during screening):
  - Routine bloods including Urea & Electrolytes, Full blood count, liver function tests (U&E, FBC, LFTs), inflammatory markers (C reactive protein (CRP)) and albumin will be measured;
  - Medical history, concomitant medications;
  - Negative tuberculosis (TB) screening per local standard of care (unless performed and documented negative in the 6 months prior to enrolment);
  - Stool examination for enteric pathogens including *Clostridium difficile*.
  - Inclusion/exclusion criteria;
  - Informed consent;
  - Mayo score (including sigmoidoscopy unless performed in previous 12 weeks, ±4 weeks);
  - Patient's weight and height and abdominal circumference.

Exclusion criteria

Subjects are excluded from the study if any of the following criteria are met at screening (visit 1) or at baseline (visit 2):

- Female subjects who are pregnant or breast feeding or considering becoming pregnant during the study.
- Patients aged <18 years.
- Patients who cannot give informed consent.
- Patients who are considered primary non-responders to anti-TNF agents.
- Contraindication to use of GLM (hypersensitivity to the active substance or to any of the excipients; active TB, acute or chronic hepatitis B infection or other severe infections such as sepsis and/or opportunistic infections including HIV infection; moderate or severe heart failure (New York Heart Association class III/IV).
- Have symptoms or signs suggestive of current active or latent TB on medical history, physical examination and/or chest radiograph, or positive *Mycobacterium tuberculosis* antigen-specific interferon-gamma release assay.
- Patients with a history of, or at imminent risk for, colectomy; who required gastrointestinal surgery within 2 months before screening.
- History of colonic mucosal dysplasia or adenomatous colonic polyps that were not removed.
- Screening stool study positive for enteric pathogens or *C. difficile* toxin.
- Oral corticosteroids at a dose >40 mg prednisone or its equivalent per day; receipt of ciclosporin, tacroli-

mus, sirolimus or mycophenolate mofetil within 8 weeks before the first study agent injection; or use of an investigational agent within five half-lives of that agent before the first study agent injection.
- Patients in recent receipt of live vaccinations within 4 weeks prior to enrolment.

Study objective

Primary objective

To ascertain if use of intensive monitoring of FCP and drug levels of GLM (during maintenance) to guide dose optimisation improves rates of pCCR and reduces disease activity in UC.

Secondary objectives

- To ascertain if the intensive monitoring of FCP and drug levels of GLM (when commenced immediately postinduction) to guide dose intensification improves rates of clinical response to induction measured at week 14 versus standard treatment doses.
- To ascertain if the intensive monitoring of FCP and drug levels of GLM (when commenced immediately postinduction) to guide dose intensification results in lower levels of measured FCP at week 46.
- To determine if intensive monitoring of GLM drug levels and FCP and concentration-based dosing leads to higher rates of corticosteroid-free remission at week 46.
- To determine if intensive monitoring of GLM drug levels and FCP and concentration-based dosing has an impact of PROs of QOL.
- To determine if intensive monitoring of drug levels and FCP with guided dose optimisation results in higher rates of mucosal healing.
- To determine if intensive monitoring of drug levels and FCP with guided dose optimisation results in differences in histological markers of inflammation using the Geboes scoring system. The Geboes scoring system has been shown to predict relapse risk.[11]

PRIMARY AND SECONDARY OUTCOME MEASURES/ END POINTS

Primary end point

Patient continuous clinical response

Absence of clinical flare, defined as an increase in modified partial Mayo score of 2 points value with accompanying requirement for treatment intervention, from week 14 through to week 46.

Secondary outcome measures

Total Mayo score

The total Mayo score is a combined endoscopic and clinical scale used to assess the severity of UC. It is a composite of subscores from four categories, including stool frequency, rectal bleeding, findings at endoscopy and physician global assessment (PGA), with a total score ranging from 0 to 12.

Partial Mayo score

Partial Mayo score consists of three subscores including stool frequency, rectal bleeding and PGA, a total score ranges from 0 to 9.

Modified partial Mayo score

A modified partial Mayo score comprises two PRO subscores, rectal bleeding and stool frequency.

Moderate-to-severe UC

Total Mayo score ≥6.

Week 14 clinical response

A decrease from Baseline (BL) in partial Mayo score by ≥30% or a decrease of 3 points.

Or

A decrease from BL in modified partial Mayo of 2 points or a decrease of ≥30% from baseline.

Clinical remission

Clinical remission is defined as a Mayo score ≤2 points, with no individual subscore >1.

Dublin score

A Dublin score is calculated as a product of the Endoscopic Mayo Score and the extent score (E1-3) of the Montreal Classification of Disease.

Clinical flare

The UC symptom recurrence as a defined by modified partial Mayo score increase of 2 points from week 14 value with accompanying requirement for treatment intervention.

Corticosteroid-free remission

Clinical remission at week 46 with no concomitant steroids.

Mucosal healing

A Mayo endoscopic subscore of 0 or 1.

Histological remission

Histological remission is defined as grade 0 in the Geboes Index.

Procedure of the study

Screening visit

Patients will be identified attending routine outpatient appointments or at time of endoscopy for investigation of IBD. A sigmoidoscopy or colonoscopy will be performed to assess disease activity and confirm a Mayo score ≥6 confirming moderate UC activity. This will be performed within 12 weeks (±4 weeks) of the first GLM injection. Only patients who have undergone TB screening per local standard of care will be deemed eligible for recruitment.

The screening visit will take place no more than 4 weeks before randomisation (day 1). Screening visit shall be carried out by an IBD nurse specialist/healthcare professional. This shall be a clinic visit. The following screening assessments shall take place:

Table 1 Schedule of events—intervention arm

Intervention group visit#	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week	−4	0	2	6	10	14	18	22	26	30	34	38	42	46
Prestudy medical screening	x													
Consent by consultant	x													
Clinical lab (haematology)	x					x								x
Clinical lab (biochemistry)	x					x								x
Clinical lab (HCG)	x													
Clinical lab (stool culture & sensitivity (C&S)	x													
Blood drawn for GLM drug levels and ADA	x			x	x	x	x	x	x	x	x	x	x	x
FCP stool sample		*x	x	x	x	x	x	x	x	x	x	x	x	x
Mayo score	x													x
Partial Mayo score						x								
Colonoscopy/sigmoidoscopy†	x													x
Short Health Scale		x	x	x	x	x	x	x	x	x	x	x	x	x
Modified partial Mayo		x	x	x	x	x	x	x	x	x	x	x	x	x
GLM drug administration by research nurse		x	x											

*Initial FCP may done at screening or baseline visit.
†Colonoscopy/sigmoidoscopy (w/Mayo score) to be completed within 12 weeks (±4 weeks) of baseline visit. Window for week 46 colonoscopy/sigmoidoscopy is also ±4 weeks.
ADA, adalimumab; FCP, faecal calprotectin; GLM, golimumab.

- Stool examination for
  - bacterial culture;
  - *C.difficile* B toxin detection.
- A stool sample for faecal calprotectin (maybe done during screening or at baseline).
- Pregnancy test (urine or serum Human Chorionic Gonadotrophin (HCG) per investigator's discretion).
- Blood collection for biochemistry and haematology (U&E, FBC, LFTs, inflammatory markers (CRP) and albumin, baseline GLM levels/antibodies).

Recording of demographics (age, gender, race/ethnicity, smoking history, alcohol history), medical history (including duration of disease and age at diagnosis), height and weight and concomitant medications. During the screening period, subjects will be evaluated for eligibility. Date of screening, subject age, gender and reason for ineligibility (if subject is not eligible) will be recorded. The results of the screening evaluation must meet the inclusion/exclusion criteria for the subject to continue in the study. Patients shall be randomised following screening into group 1 (SMPC arm) or group 2 (intervention arm); schedule of visits is provided in table 1 and 2.

Group 1—SMPC arm

At each hospital visit:

- eligibility check;
- assessment of efficacy outcome measures;
- assessments of safety (adverse event monitoring);
- recording of concomitant medications;
- assessment of compliance with study medications.

Hospital visit week 0—nurse to educate self-administration of GLM in the clinic.

Hospital visit week 2—nurse to educate self-administration of GLM in the clinic.

Hospital visit at week 14—vital signs and weight to be recorded in CRF and medical record. Assessment of response to GLM induction will be measured by a partial Mayo score, which will include assessment by physician. A stool sample for FCP, routine bloods including LFTs, albumin, FBC and inflammatory markers (CRP) shall be measured. GLM drug levels and antibodies to GLM shall also be taken. GLM levels shall be measured by ELISA supplied by IDKMonitor. In accordance with the SMPC for GLM, continued therapy shall be reconsidered in patients who show no evidence of therapeutic benefit within 14 weeks.

Hospital visit at week 46—vital signs weight and abdominal circumference to be recorded in CRF and medical record. Assessment of mucosal healing/Mayo score—the patient will attend the hospital and have a repeat sigmoidoscopy/colonoscopy performed. They will be assessed by a doctor. A stool sample for FCP, routine bloods including LFTs, albumin, FBC and inflammatory markers (CRP) shall be measured. GLM drug levels and antibodies to GLM shall also be taken.

Table 2 Schedule of events—SMPC arm

SMPC arm visit#	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week	−4	0	2	6	10	14	18	22	26	30	34	38	42	46
Prestudy medical screening	x													
Consent by consultant	x													
Clinical lab (haematology)	x					x								x
Clinical lab (biochemistry)	x					x								x
Clinical lab (HCG)	x													
Clinical lab (stool C&S)	x													
	x													
Blood drawn for GLM drug levels and ADA	x					x								x
FCP stool sample		*x				x								x
Mayo score	x													x
Partial Mayo score						x								
Colonoscopy/ sigmoidoscopy†	x													x
Short Health Scale		x	x	x	x	x	x	x	x	x	x	x	x	x
Modified partial Mayo		x	x	x	x	x	x	x	x	x	x	x	x	x
GLM drug administration by research nurse		x	x											

*Initial FCP may done at screening or baseline visit.
†Colonoscopy/sigmoidoscopy (w/Mayo score) to be completed within 12 weeks (±4 weeks) of baseline visit. Window for week 46 colonoscopy/sigmoidoscopy is also ±4 weeks.
ADA, adalimumab; FCP, faecal calprotectin; GLM, golimumab.

WEEKS 6, 10, 18, 22, 26, 30, 34, 38, 42, 46

Patients shall fill out a PRO on a mobile app/paper form that will assess QOL and symptoms of bleeding/diarrhoea. This will also allow them to request contact from the IBD service.

Early withdrawal (if necessary)—week 14 procedures will be completed. Sigmoidoscopy/colonscopy to be performed at discretion of investigator.

Group 2—intervention arm

At each hospital visit:

- eligibility check;
- assessment of efficacy outcome measures;
- assessments of safety (adverse event monitoring);
- recording of concomitant medications;
- assessment of compliance with study medications.

Hospital visit week 0—nurse to educate self-administration of GLM in the clinic.

Hospital visit week 2—nurse to educate self-administration of GLM in the clinic.

Hospital visit at week 14—vital signs and weight to be recorded in CRF and medical record. Assessment of response to GLM induction will be measured by a partial Mayo score, which will include assessment by physician. A stool sample for FCP, routine bloods including LFTs, albumin, FBC and inflammatory markers (CRP) shall be measured. GLM drug levels and antibodies to GLM shall also be taken. In accordance with the SMPC for GLM, continued therapy shall be reconsidered in patients who show no evidence of therapeutic benefit within 14 weeks.

Hospital visit at week 46—vital signs, weight and abdominal circumference to be recorded in CRF and medical record. Assessment of mucosal healing/Mayo score—the patient will attend the hospital and have a repeat sigmoidoscopy/colonoscopy performed. They will be assessed by a doctor. A stool sample for FCP, routine bloods including LFTs, albumin, FBC and inflammatory markers (CRP) shall be measured. GLM drug levels and antibodies to GLM shall also be taken (see table 2).

WEEKS 6, 10, 18, 22, 26, 30, 34, 38, 42, 46

Patients shall fill out a PRO on a mobile app/paper form that will assess QOL and symptoms of bleeding/diarrhoea. The patient shall also leave a stool sample for FCP and attend the hospital for a blood test to be performed prior to taking GLM. The dose of GLM shall be adjusted according to the FCP and drug level of GLM (table 3). The patient shall be contacted by the IBD service regarding what dose of GLM to self-administer. These visits do not include being seen by a physician and thus the frequency of hospital visits where the patient is assessed by a physician is equal in both groups.

Table 3 Dose optimisation algorithm

FCP level	DL <2.5	DL >2.5	DL 4–6.5	DL >6.5
>250	Increase dose by 50 mg every 4 weeks until DL >4	Increase dose by 50 mg every 4 weeks until DL >4	Maintain dose	Maintain dose
50–250	Increase dose by 50 mg every 4 weeks until DL >2.5	Maintain dose	Maintain dose	*Reduce dose by 50 mg
<50	Maintain dose	Maintain dose	Reduce dose	*Reduce dose by 50 mg

DL, drug levels; FCP, faecal calprotectin.

GLM dose shall not be increased to a dose >200 mg. A dose of 200 mg GLM shall not be administered more than three consecutive times. If patients are symptomatic and FCP levels remain elevated, patients shall be evaluated by sigmoidoscopy and alternative treatment shall be administered at treating physician's discretion (intravenous anti-TNF/intravenous steroids/vedolizumab/surgery). If patients remain asymptomatic but FCP levels remain elevated, endoscopy at the physician's discretion shall be performed and GLM shall be reduced by 50 mg and the patient will continue to be monitored.

*if a patient has an FCP level between 50 and 250 or <50 and DL between 4 and 6.5 or >6.5 and is already on the minimum dose of 50 mg, that dose will be continued.

Informed consent shall be obtained prior to any endoscopic procedure.

Early withdrawal (if necessary)—week 14 procedures will be completed. Sigmoidoscopy/colonscopy to be performed at discretion of investigator.

SAMPLE SIZE

Sample size was estimated to determine the superiority of the intervention over treatment-as-usual, with respect to rates of sustained response (pCCR).

Based on the results of previous studies, the treatment-as-usual group are projected to experience rate of clinical response of approximately 65% by week 14, of whom 50% will have a sustained response (CCR) from there to week 46, amounting to a 32.5% CCR rate. An increase of 25 percentage points in the rate of pCCR would be considered clinically significant. Sample size calculations based on a superiority Z-test showed that a sample size of 112 patients would be required to ensure a power of at least 85%, at a 5% significance level, to detect pCCR rate of 25 percentage points higher or more for patients receiving the intervention compared with those on treatment-as-usual. Adjusting this sample size for an expected dropout rate of 20% gives a total required sample size of 136 (adding one patient to ensure balanced treatment group sizes).

ANALYSIS SETS

Table 4 defines the sets of subjects whose data are to be included in the statistical analyses.

Analysis of efficacy end points will be carried out on patients of the full analysis set and on patients of the per-protocol set for sensitivity analyses.

For the primary efficacy end point, pCCR, the following analysis will be carried out:

- Descriptive analysis comparing the percentage of patients that achieve pCCR between control and treatment groups. Ratios of relative risk will be presented with 95% CIs for each group.
- A superiority Z-test will be carried out to investigate whether the rate of pCCR is higher for patients receiving the intervention than for patients in the treatment-as-usual group.
- A logistic regression model will assess the effect of the intervention on the rate of pCCR, adjusting for measured covariates of interest, including age, gender, BMI, smoking status and concomitant use of immunomodulators.

Binary secondary end points (moderate-to-severe UC, week 14 clinical response, clinical remission, clinical flare, corticosteroid-free remission, mucosal healing) will be analysed by:

- comparing percentages for treatment-as-usual and intervention groups;
- calculating ratios of relative risk with 95% CIs, for comparison of treatment-as-usual and intervention groups;
- conducting superiority Z-tests tests, to determine whether the risk of each end point is higher (or lower, where relevant) for patients on the intervention, compared with patients on treatment-as-usual;

Table 4 Data analysis sets

Randomised set	All randomised patients
Full analysis set (based on intention to treat (ITT) principle)	Randomised patients having the studied disease, having taken at least one dose of study treatment after inclusion and with at least one evaluation of the primary criteria.
Per-protocol set	Patients of the full analysis set without relevant deviation, which could affect the evaluation of efficacy outcome.
Safety set	All patients having received at least one dose of the treatment.

- logistic regression models to determine whether the odds of each end point occurring differs between intervention and treatment-as-usual, adjusting for measured covariates of interest.

Numeric secondary end points (total Mayo score, partial Mayo score, modified partial Mayo score) will be analysed by:

- comparing descriptive statistics on the end points for intervention and treatment-as-usual groups;
- linear regression modelling to assess the effect of the intervention on each end point and to adjust for, and to assess, the effects of any measured covariates of interest on each end point; or where assumptions of regression are violated, non-parametric modelling will be applied.

PATIENT RECORDS

Data are collected via an e-CRF and stored in a secured database. Participants will be identified by a study-specific number in the database. The name and any other identifying detail will not be included in any study data electronic file. Essential documents will be retained until at least 15 years after the publication of the clinical study report.

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Funding This work was supported by an IIS grant from MSD IISP #: 53428.

Competing interests None declared.

Ethics approval St. Vincent's University Hospital Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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