**“Vedolizumab Immunomodulator Enforced Withdrawal Study (VIEWS Study)”**

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| Version No | 8 |
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**PROTOCOL OUTLINE**

|  |  |
| --- | --- |
| **Title** | Vedolizumab Immunomodulator Enforced Withdrawal Study (VIEWS Study) |
| **Source of recruitment** | IBD-centres within Australia |
| **Endpoints** | Primary Endpoints* Vedolizumab trough levels in the treatment groups (Thiopurine-continue and thiopurine-withdrawal) at week 48

Secondary Endpoints* Steroid-free clinical remission (partial Mayo score ≤ 2 with no item > 1) in the treatment groups at week 48
* Steroid-free endoscopic remission (Mayo endoscopic score of 0 or 1, with no increase in Mayo endoscopic score from 0 to 1 at week 48) in the treatment groups at week 48
* C-reactive protein level in the treatment groups
* Faecal calprotectin level in the treatment groups
* Diseases flares in the treatment groups
* Adverse events in the treatment groups
 |
|  |  |
| **Design** | Phase IV, multi-centre, randomised controlled study.  |
|  |  |
| **Population** | Patients with a confirmed diagnosis of ulcerative colitis in steroid-free clinical remission for at least 6 months and on combination therapy with vedolizumab and thiopurine (either azathioprine or mercaptopurine) for at least 6 months |
|  |  |
| **Sample size** | 65 patients will be recruited into the study  |
|  |  |
| **Efficacy assessments** | * Mayo score
* Faecal calprotectin
* Blood tests
 |
| **Scientific studies** | * Blood tests (vedolizumab trough level, anti-vedolizumab antibody level, FBC, UEC, LFT, CRP, ESR)
 |
| **Safety data** | * Adverse event reports
* Blood tests (standard haematology, serum chemistry)
* Urine pregnancy
* Physical examination
* Withdrawals and compliance
 |
| **Statistical procedures** | Study endpoints will be primarily assessed using ‘intention to treat’ (ITT) analysis; however ‘per protocol’ analysis will also be performedPredicted vedolizumab levels:* Thiopurine-withdrawal: 5.2 μg/mL
* Thiopurine-continue: 8.8 μg/mL

Power analysis: assuming a standard deviation of 4.5 μg/mL, and enrolling patients in a 2:1 ratio, the study would require 39 patients in the thiopurine-withdrawal group and 20 patients in the thiopurine-continue group to achieve a power of 80% and a level of significance of 5% (two-sided), for detecting a true difference in the means between the two groups of 3.6 (8.8 – 5.2) μg/mL. To account for drop-outs, an extra 6 (10%) patients will be recruited. Hence a total of 65 patients will be required for the study. |
| **Study duration & dates** | Total of 42 month recruitment period from June 2018 – December 2021 |

**Study Schedule**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Procedure** | **Screening** (-12 weeks) | **Week 0****(+/- 1 week)** | **Week 8****(+/- 1 week)** | **Week 16****(+/- 1 week)** | **Week 24****(+/- 1 week)** | **Week 32****(+/- 1 week)** | **Week 40****(+/- 1 week)** | **Week 48****(+/- 1 week)** | **Clinical Relapse**  | **2yr FU** |
| Consent | X |  |  |  |  |  |  |  |  |  |
| Inclusion/ Exclusion | X | X |  |  |  |  |  |  |  |  |
| Demography | X |  |  |  |  |  |  |  |  |  |
| Medical History | X |  |  |  |  |  |  |  |  | X2 |
| Partial Mayo Score |  | X | X | X | X | X | X |  | X | X |
| Total Mayo Score | X1 |  |  |  |  |  |  | X1 | X | X 2 |
| Physical Examination | X |  |  |  |  |  |  | X | X | X2 |
| Blood tests FBCEUCESR LFTCRP | X | X | X | X | X | X | X | X | X | X2 |
| Blood tests6TGN & 6MMP levels | X | X |  |  | X |  |  | X | X | X |
| Vedolizumab 3* Concentration
* Anti-Vedo Ab
 |  | X | X For storage, test only in pt that flare | X For storage, test only in pt that flare | X |  |  | X | X | X |
| Urine pregnancy test 4 | X | X | X | X | X | X | X | X |  |  |
| Faecal Calprotectin |  | X |  |  | X |  |  | X | X |  |
| Sigmoidoscopy (screening scope within 12 weeks of randomisation) | X |  |  |  |  |  |  | X | X |  |
| Adverse Effects and flares |  |  | X | X | X | X | X | X | X | X2 |
| Stool Culture and *Cl.difficile* testing |  |  |  |  |  |  |  |  | X |  |

1 After sigmoidoscopy

2 Retrospective data collection if procedure has been completed after the week 48 visit

3 Prior to vedolizumab infusion (-1 to 0 day)

4.Screening pregnancy test is mandatory, following tests as per site SOC

**ABBREVIATIONS AND DEFINITIONS**

AE Adverse Event

DSMB Data Safety Monitoring Board

GCP Good Clinical Practice

IBD Inflammatory Bowel Disease

ITT Intention To Treat

PP Per Protocol

SAE Serious Adverse Event

UC Ulcerative colitis

VDZ Vedolizumab

6TGN 6-thioguanine nucleotide

6MMP 6-methylmercaptopurine

1. **INTRODUCTION**

Ulcerative colitis (UC) is a chronic inflammatory disorder of the large intestine that is characterised by symptoms of bloody diarrhoea, urgency and abdominal pain. Treatment modalities include corticosteroids, aminosalicylates, immunomodulators and biologic agents, and combination therapy may be needed to achieve remission.

Combination therapy using thiopurines and anti-TNFα agents has been shown to be more effective than monotherapy in the treatment of UC [1]. Concomitant thiopurine use also reduces antibody formation to anti-TNFα agents and assists in maintaining adequate circulating drug levels [2]. However due to concerns about adverse effects associated with combination therapy (including infections, skin cancers and lymphoma), patients and clinicians may consider withdrawing thiopurine usage once remission is achieved, leaving patients on biologic monotherapy.

Vedolizumab is a monoclonal antibody that selectively inhibits the binding of the α4β7-integrin to mucosal addressin cell adhesion molecule-1 (MADCAM-1) which is preferentially expressed in the intestinal endothelium [3]. This interferes with the migration of inflammatory cells into the gastrointestinal tract. The GEMINI 1 trial demonstrated the effectiveness of vedolizumab in the treatment of ulcerative colitis [4]. However *post hoc* analyses did not reveal any additional benefit with combination therapy, both at week 6 and 52 [5]. Hence the benefit of combination therapy with vedolizumab, as opposed to anti-TNFα agents, is less clear. Also, there is a lack of data on the effect of thiopurine withdrawal on vedolizumab trough levels and titres of vedolizumab antibodies.

The aim of our study is to determine whether thiopurine withdrawal after 6 months of combination therapy with vedolizumab in UC patients with steroid-free clinical remission impacts upon their vedolizumab trough levels and anti-vedolizumab antibody titres.

1. **STUDY OBJECTIVES**

**2.1 Primary Endpoints**

1. Comparing the change in vedolizumab trough level in the thiopurine-continue versus the thiopurine-withdrawal group at week 48
2. Comparing the change in anti-vedolizumab antibody level in the thiopurine-continue group versus the thiopurine-withdrawal group at week 48

**2.2 Secondary Endpoints**

1. Proportion of patients who remained in steroid-free clinical remission (partial Mayo score ≤ 2 with no item > 1) in the thiopurine-continue group versus the thiopurine-withdrawal group at week 48
2. Proportion of patients who had a disease flare [partial Mayo score ≥ 3 and faecal calprotectin > 150 μg/g or Mayo endoscopic score ≥ 2 (or increase from 0 to 1)] in the thiopurine-continue group versus the thiopurine-withdrawal group
3. Proportion of patients who required corticosteroid therapy (either oral or rectal) for a disease flare in the thiopurine-continue group versus the thiopurine-withdrawal group
4. Proportion of patients who remained in endoscopic remission (Mayo endoscopic score of 0 or 1, with no increase in Mayo endoscopic score from 0 to 1 at week 48) in the thiopurine-continue group versus the thiopurine-withdrawal group at week 48
5. Proportion of patients who remained in both clinical and endoscopic remission (as defined in points 1 and 2 above) in the thiopurine-continue group versus the thiopurine-withdrawal group at week 48
6. Proportion of patients in histological remission in the thiopurine-continue group versus the thiopurine-withdrawal group at week 48
7. Proportion of patients in histological-endoscopic remission (combined histological and endoscopic remission) in the thiopurine-continue group versus the thiopurine-withdrawal group at week 48
8. Comparing the change in faecal calprotectin level in the thiopurine-continue group versus the thiopurine-withdrawal group
9. Comparing the change in C-reactive protein level in the thiopurine-continue group versus the thiopurine-withdrawal group
10. Adverse events in the thiopurine-continue group versus the thiopurine-withdrawal group
11. **STUDY DESIGN**

This is a Phase IV, multi-centre, randomised controlled study assessing thiopurine withdrawal in patients on combination therapy with vedolizumab.

Once consent has been obtained and the patient has met all the inclusion criteria with no exclusions, the patients will be enrolled into the study.

Patients will be randomised into one of two arms in a 2:1 ratio:

1. Continue scheduled vedolizumab and discontinue thiopurine therapy (“thiopurine-withdrawal”)
2. Continue scheduled vedolizumab and continue thiopurine therapy at the same dosage (“thiopurine-continue”)

Patients will be monitored every 8 weeks (during their vedolizumab infusion dates) up to a total of 48 weeks. A 2year post study follow up will assess for clinical relapses and vedolizumab levels

1. **SELECTION OF STUDY POPULATION**

**4.1 Study population**

The study population will consist of patients with ulcerative colitis in steroid-free clinical remission for at least 6 months. They will be on combination therapy with vedolizumab and a thiopurine for at least 6 months prior to enrolling.

**4.2 Inclusion Criteria**

|  |
| --- |
| **Patients must meet all the following INCLUSION CRITERIA at enrolment to be eligible to participate** |
| 1. Age > 18 years
 |
| 1. Ulcerative colitis
 |
| 1. Steroid-free clinical remission for at least 6 months
 |
| 1. Treated with a combination of vedolizumab and a thiopurine for at least the preceding 6 months
 |
| 1. Scheduled administration of vedolizumab 300mg every 8 weeks during the preceding 6 months
 |
| 1. Appropriate and stable dose of thiopurine for the preceding 3 months
 |
| 1. Appropriate dose of thiopurine is defined as:
2. Azathioprine: maintenance dose of 2-2.5mg/kg/day OR 6TGN level > 235 pmol/8 × 108 erythrocytes OR the maximally tolerated dose
3. Mercaptopurine: maintenance dose of 1-1.5mg/kg/day OR 6TGN level > 235 pmol/8 × 108 erythrocytes OR the maximally tolerated dose
 |
| 1. Mayo endoscopic score 0 or 1 at baseline in the 12 weeks preceding randomisation
 |
| 1. Contraceptive use during the whole study for childbearing female patients
 |
| 1. Provide written informed consent to participate as shown by a signature on the consent form
 |

If any item is answered NO, then the patient is NOT ELIGIBLE to participate in this study.

**4.3 Exclusion Criteria**

 The patient must be excluded for any of the following reasons:

|  |
| --- |
| **Patients must not meet any of the following EXCLUSION CRITERIA at enrolment to be eligible to participate** |
| 1. Consent not obtained or unable to give informed consent
 |
| 1. Unable to communicate with the investigators and comply with the study requirements
 |
| 1. Females who are pregnant or actively trying to fall pregnant
 |
| 1. Patients unwilling to practice an effective method of contraception throughout the study period
 |
| 1. Patients with an ostomy or ileoanal pouch
 |
| 1. Patients who had used steroid therapy in the last 6 months prior to screening
 |
| 1. A diagnosis of Crohn’s disease or indeterminate colitis
 |
| 1. Other biologic use (not vedolizumab), Janus kinase (JAK) inhibitor use or other trial therapies in the last 6 months prior to screening
 |

**4.4 Permitted Medications**

All medications used for ulcerative colitis (except for thiopurine according to study design) must be kept at stable dosages throughout the study.

**4.5 Excluded Medications**

 Study patients are excluded from taking the following medications:

* Oral and rectal steroids are not permitted for 6 months prior to entering the study and are not permitted during the study period (use of topical or inhaled steriods for other conditions are permitted)
* No other biologic use asides vedolizumab is allowed during the course of the study or the preceding 6 months

**4.6 Recruitment**

Patients will be recruited from IBD-centres in Australia. All eligible patients who are willing to participate will be informed about the study, given a study participant information sheet to read, and offered the opportunity to ask questions before signing an informed consent form. Paticipant characteristics will be recorded on the case report form that contains information pertaining to (but not limited to) age, sex, medical history and concurrent medications.

Patients who fail the inclusion/exclusion criteria at screening will be informed that they are not eligible for inclusion into the study and will be treated by the Investigator as per standard clinical practice.

**4.7 Randomisation**

Recruited study paticipants will be randomised in a 2:1 ratio to either continue vedolizumab and stop thiopurine, or continue vedolizumab/thiopurine therapy at same dosage. Randomisation will occur using a computer generated program.

**4.8 Number of Participants**

A total of 65 patients are to be enrolled across the involved IBD centres.

1. **STUDY PROCEDURE AND SCHEDULE**

 **STUDY DESIGN FLOW DIAGRAM**

**Screening**

History

Examination

Demographics

Trial Criteria

Blood tests

Urine dipstick

Sigmoidoscopy

Mayo score

Consent

RANDOMISATION *2:1 ratio*

**Group 1: Continue vedolizumab and stop thiopurine**

**Group 2: Continue vedolizumab and thiopurine**

**Week 0**

Total Mayo score

Blood tests with:6TGN, 6MMP levels

Vedo level/antibodies

Faecal calprotectin

**Week 8, 16**

pMayo score

Blood tests

**Week 24**

pMayo score

Blood tests with:

6TGN/6MMP levels

Vedo level/antibodies

Faecal calprotectin

**Week 32, 40**

pMayo score

Blood tests

**Week 48**

Total Mayo score

Blood tests with:

6TGN/6MMP levels

Vedo level/antibodies

Faecal calprotectin

Sigmoidoscopy +/- 2wks

**Week 0**

Total Mayo score

Blood tests with:

6TGN, 6MMP levels

Vedo level/antibodies

Faecal calprotectin

**Week 8, 16**

pMayo score

Blood tests

**Week 24**

pMayo score

Blood tests with:

Vedo level/antibodies

6TGN/6MMP levels

Faecal calprotectin

**Week 32, 40**

pMayo score

Blood tests

**Week 48**

Total Mayo score

Blood tests with:

Vedo level/antibodies

6TGN/6MMP levels

Faecal calprotectin

Sigmoidoscopy +/- 2wks

**2-year follow-up**

History +/- exam

Blood tests

Vedo level

Sigmoidoscopy

Mayo score

**2-year follow-up**

History +/- exam

Blood tests

Vedo level

Sigmoidoscopy

Mayo score

**Clinical relapse**

pMayo

Sigmoidoscopy

F. calprotectin

Blood tests

Vedo level/Ab

Stool culture

**Clinical relapse**

pMayo

Sigmoidoscopy

F. calprotectin

Blood tests

Vedo level/Ab

Stool culture

**5.1. Study Diagnostics**

A combination of blood, stool and colonic biopsy testing, along with disease activity indices, will be used to collect study data.

**5.1.1. Blood tests**

 Study patients will undergo blood testing at the following standard of care time points:

* Screening
* Week 0
* Week 8
* Week 16
* Week 24
* Week 32
* Week 40
* Week 48
* Clinical relapse
* 2yr FU (results recorded retrospecitivly)

At all of these time points, blood will be collected for:

* + Routine tests to assess for disease activity and potential adverse events
		- FBC, UEC, LFT, CRP, ESR

At screening, week 0, week 24 and week 48, clinical relapse and 2yr FU blood will also be collected for:

* + 6TGN and 6MMP levels.
	+ Vedolizumab trough level and anti-vedolizumab antibody level

(See Appendix 2)

**5.1.2. Stool tests**

Study patients will undergo stool testing for faecal calprotectin at the following standard of care time points:

* Week 0, Week 24, Week 48 and at clinical relapse

**5.1.3. Endoscopic tests**

Study patients will undergo a flexible sigmoidoscopy at the following time points:

* + Screening (if completed within 12 weeks of randomisation does not need to be repeated)
	+ Week 48
	+ Clincial relapse
	+ 2yr FU (results recorded retrospectivly if done as SOC)

At these time points for the flexible sigmoidoscopy, the following will occur:

* Preparation: as per local requirements
* The sigmoidoscopy will be performed to a minimum of 30cm and when formed stool is encountered that does not permit further passage of the endoscope
* Photographs will be taken for endoscopic assessment and gross mucosal assessments from the rectum and sigmoid colon, with the worst affected area identified and photographed
* Colonic tissue/biopsies (at least 2 biopsies) from the most inflamed area of bowel will be collected for histopathology to assess disease activity. If there is no inflamed area, then biopsies should be taken from 20cm – 30cm. Slides will be prepared as per local practice. They will be sent to a central site (Concord Hospital) for a blinded review by a pathologist.\*
* Endoscopic evaluation of mucosal appearance will be used to calculate:
	+ Endoscopic component of the Total Mayo score
* Endoscopic assessment for the purpose of Total Mayo score should be based on the worst affected area of bowel examined

\* The biopsies will not be sent in a de-identified form. Study team will not have access or view the slides, only the central reading pathologist. The pathologist will send the scores back to the original site. The study coordinator at each site can then enter the data for their participants on the CRF. Biopsies are packed as per local SOP and shipped ambient temperature to Concord RGH.

**5.1.4. Disease activity: Mayo Score**

Ulcerative colitis disease activity will be formally calculated using the Mayo scoring system (see Appendix 1)

Endoscopic assessment for the purpose of Total Mayo score should be based on the worst affected area of bowel examined.

Mayo Score

The Mayo score is a well-established internationally accepted and standardised scoring system that provides clinical and endoscopic criteria for assessment of UC disease activity [7]. The Mayo score ranges from 0-12, with higher scores indicating more severe disease. It will be used to measure participant UC disease activity at particular time points during the course of the study.

A Total Mayo score is calculated using both clinical and endoscopic criteria.

This will be calculated at the following time points in the study when patients undergo endoscopic evaluation:

* + Screening
	+ Week 48
	+ Clinical relapse
	+ 2yr FU (if result available)

A Partial Mayo score is calculated using only the clinical criteria in the absence of endoscopy (score ranges from 0-9). This will be calculated at all scheduled study visits:

* Week 0
* Week 8
* Week 16
* Week 24
* Week 32
* Week 40
* Week 48
* Clinical relapse
* 2yr FU (results recorded retrospectively)

**5.2 Description of Study Days/Visits**

 Scheduled study visits for study patients are as listed.

 ***Screening Period (-12weeks to Day 0)***

At this visit the patient will be approached regarding the study and assessed for suitability with collection of baseline data / information. The patient will undergo the following assessments:

* Informed consent obtained
* Medical history
* Medication history (current/baseline and previous)
* Demographic data (age, gender)
* Inclusion & Exclusion criteria
* Physical examination
* Flexible sigmoidoscopy
* Total Mayo score (includes the screening flexible sigmoidoscopy)
* Urine pregnancy test if female of childbearing potential (If pregnancy test is positive, the patient will be ineligible for the study)
* Blood tests (FBC, UEC, LFT, CRP, ESR, 6TGN, 6MMP)

***Week 0 – Study Visit 1***

The patient will undergo the following assessments/collection of data:

* Confirm patient meets inclusion and exclusion criteria for the study
* Partial Mayo score
* Patient will undergo randomization prior to their vedolizumab infusion
* Blood tests to be performed prior to vedolizumab infusion:
	+ Vedolizumab trough level/anti-vedolizumab antibody blood test performed
	+ FBC, UEC, LFT, CRP, ESR
	+ 6TGN and 6MMP levels
* Faecal calprotectin
* Urine dipstick pregnancy test (if applicable)

***Week 8 – Study Visit 2***

The patient will undergo the following assessments/collection of data:

* Partial Mayo score
* Blood tests to be performed:
	+ FBC, UEC, LFT, CRP, ESR
* Urine dipstick pregnancy test (if applicable)
* Assess for adverse events or disease flare

***Week 16 – Study Visit 3***

The patient will undergo the following assessments/collection of data:

* Partial Mayo score
* Blood tests to be performed:
	+ FBC, UEC, LFT, CRP, ESR
* Urine dipstick pregnancy test (if applicable)
* Assess for adverse events or disease flare

***Week 24 – Study Visit 4***

The patient will undergo the following assessments/collection of data:

* Partial Mayo score
* Blood tests to be performed prior to vedolizumab infusion:
	+ Vedolizumab trough level/anti-vedolizumab antibody blood test performed
	+ FBC, UEC, LFT, CRP, ESR
	+ 6TGN and 6MMP levels
* Faecal calprotectin
* Urine dipstick pregnancy test (if applicable)
* Assess for adverse events or disease flare

***Week 32 – Study Visit 5***

The patient will undergo the following assessments/collection of data:

* Partial Mayo score
* Blood tests to be performed:
	+ FBC, UEC, LFT, CRP, ESR
* Urine dipstick pregnancy test (if applicable)
* Assess for adverse events or disease flare

***Week 40 – Study Visit 6***

The patient will undergo the following assessments/collection of data:

* Partial Mayo score
* Blood tests to be performed:
	+ FBC, UEC, LFT, CRP, ESR
* Urine dipstick pregnancy test (if applicable)
* Assess for adverse events or disease flare

***Week 48 – Study Visit 7***

The patient will undergo the following assessments/collection of data:

* Flexible sigmoidoscopy within one week +/- the week 48 infusion
* Total Mayo score
* Blood tests to be performed prior to vedolizumab infusion:
	+ Vedolizumab trough level/anti-vedolizumab antibody blood test performed
	+ FBC, UEC, LFT, CRP, ESR
	+ 6TGN and 6MMP levels
* Faecal calprotectin
* Urine dipstick pregnancy test (if applicable)
* Assess for adverse events or disease flare

**Clinical relapse**

The patient will undergo the following assessments/collection of data:

* Flexible sigmoidoscopy
* Total Mayo score
* Blood tests to be performed:
	+ Vedolizumab trough level/anti-vedolizumab antibody blood test
	+ FBC, UEC, LFT, CRP, ESR
	+ 6TGN and 6MMP levels
* Faecal calprotectin
* Stool culture
* Assess for adverse events or disease flare

***2yr Follow Up***

The patient will undergo the following assessments/collection of data:

* Flexible sigmoidoscopy (if the test has been performed as SOC, data will be collected retrospectively. If no scope has been performed, no data wil be collected)
* UC related medical history/adverse events will be collected retrospectively to assess for flares, UC medication changes and surgery post the week 48 visit
* Blood test results from the most recent SOC collection will be recorded (no blood collection specifically for the visit)
* Blood tests to be performed prior to vedolizumab infusion (closest to 2yr point):
	+ Vedolizumab trough level/anti-vedolizumab antibody blood test performed
1. **ADVERSE EVENTS**

**6.1 Definitions**

**6.1.1 *Adverse Event***

The term adverse event (AE) covers any sign, symptom, syndrome, or illness that appears or worsens in a participant during the period of observation in the clinical study and that may impair the well-being of the participant. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study). Undesirable experiences including intercurrent events (or diseases), drug reactions and clinical abnormalities or clinically significant laboratory test abnormalities that occur during the course of a trial are also included.

The AE may be:

* A new illness
* Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
* Unrelated to participation in the clinical study
* A combination of one or more of these factors
	+ Thus, no causal relationship with the study medication/therapy is implied by the use of the term “adverse event”. Surgical/endoscopic procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event. Planned surgical/endoscopic procedures permitted by the study protocol and the conditions leading to these procedures are not adverse events. (See Appendix 4 - Definitions of causality and severity of adverse events).
	+ Adverse events will be recorded at all scheduled study visits. The investigator will assess and record any adverse event in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study procedure, if known, and any action(s) taken.

**6.1.2 *Serious* *Adverse Event***

If an adverse event meets any of the following criteria, it is regarded as serious adverse event (SAE) and should be reported within 24 hours of the site being made aware of the serious adverse event to the principal investigators.

* **Death of Participant**
	+ An event that results in the death of a participant.
* **Life-Threatening**
	+ An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
* **Hospitalization**
	+ An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
* **Prolongation of** **Hospitalization**
	+ An event that occurs while the study participant is hospitalized and prolongs the participant’s hospital stay.
* **Persistent or Significant Disability/Incapacity**
	+ An event that results in a condition that substantiallyinterferes with the activities of daily living of a studyparticipant. Disability is not intended to include experiences ofrelatively minor medical significance such as headache,nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle).
* **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome**
	+ An important medical event that may not be immediatelylife-threatening or result in death or hospitalization, butbased on medical judgment may jeopardize the participant andmay require medical or surgical intervention to prevent anyof the outcomes listed above (i.e., death of participant,life-threatening, hospitalization, prolongation ofhospitalization, congenital anomaly, or persistent orsignificant disability/incapacity). Examples of such eventsinclude allergic bronchospasm requiring intensive treatmentin an emergency room or at home, blood dyscrasias orconvulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs will be reported and assessed by the investigator in terms of severity and relationship to the study medication/therapy. The outcome of the adverse event as well as the measures taken as a result of this event will be described and the principal investigators will be informed.

**6.1.3 Definitions of AE Severity**

The investigator will use the following definitions to rate the severity of each adverse event:

* **Mild** The adverse event is transient and easily tolerated by the participant.
* **Moderate** The adverse event causes the participant discomfort and interrupts the participant's usual activities.
* **Severe** The adverse event causes considerable interference with the participant’s usual activities and may be incapacitating or life-threatening.

**6.1.4 Relationship to Medication/Procedures**

The investigator will use the following definitions to assess the relationship of the adverse event to the use of drug:

* **Probably Related** An adverse event has a strong temporal relationship to drug or recurs on re-challenge and other cause of event is unlikely or significantly less likely.
* **Possibly Related** An adverse event has a strong temporal relationship to the drug and another cause of event is equally or less likely compared to the potential relationship to drug.
* **Unlikely:** An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

The patients will be specifically assessed for infection and malignancies and the incidence rates of these events will be presented as descriptive summary statistics and the number and percentage of patients who experience adverse events will be tabulated.

1. **WITHDRAWALS AND TREATMENT FAILURES**

**7.1 Treatment Failures**

Participants may be deemed treatment failures for any of the following reasons:

* Partial Mayo score ≥ 3 and/or faecal calprotectin > 150 μg/g or increase of Mayo endoscopic score from baseline
* Need for rescue medications (any new UC medication/s, including steroids, or increased dose of baseline medications)
* Surgical intervention for the treatment of UC
* Patients who have an infusion/treatment-related adverse event leading to discontinuation or dose/frequency change of vedolizumab or thiopurine

**If a patient requires a change in medications due to treatment failure at any point between screening and week 48 the following should occur.**

* **Patient is discontinued from active study and treated as per local investigator**
* **Procedues as per table in study schedule for clinical relapse**
* **Complete 2 yr FU visit at 2yrs post withdrawal (unless patient withdraws consent)**

**7.2 Withdrawal of participants**

 Participants may be withdrawn from the study for the following reasons:

* At their own request
* If, in the investigators opinion, continuation in the study would be detrimental to the participants well-being. The investigator also has the right to withdraw patients from the trial if it is felt that it is in the best interests of the patient.
* At the specific request of the Investigator.
* If the participant is less than 80% compliant with study therapy and/or testing
* If the participant requires an escalation in therapy for UC during the course of the study – deemed treatment failure
* If the participant becomes pregnant

In all cases of participant withdrawal, the reason for withdrawal must be recorded. The participant must be followed up till resolution of Adverse Events.

Participants can continue in the study if they suffer an adverse event that is not believed to warrant withdrawal.

1. **EMERGENCY PROCEDURES**

**8.1 Emergency Contact**

In emergency situations, the responsible principal investigator for a clinical study site and/or the Research Coordinator should be contacted by telephone using the number listed on the corresponding “Patient Information & Consent Sheet” for that particular clinical site. All clinical site principal investigators will also be contactable at all times for emergency situations via the hospital switchboard of their relevant institution.

**8.2 Emergency treatment**

During and following a participants participation in the trial, the investigator / institution will ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator / institution will also inform the participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

1. **STATISTICAL PROCEDURES**

**9.1 Analysis variables**

The primary outcome of the trial is comparing the change in vedolizumab trough levels between the two groups.

Secondary outcomes relate to steroid-free clinical and endoscopic remission rates, biochemical parameters in the C-reactive protein and faecal calprotectin levels.

Descriptive statistics will be computed for all variables using means, standard deviations, medians, interquartile ranges, and percentiles for continuous factors and frequencies for categorical variables. These will be used to examine the distribution of study variables, to identify outliers, and to determine variable categorization.

Two-tailed Fisher exact tests will be used to test for difference between proportions and Kruskal–Wallis and Mann–Whitney tests for nonparametric observations. Univariate analysis will be used to test for predictive values with Bonferroni correction for multiple comparisons. Kaplan–Meier analysis with log-rank statistics will be performed to test for maintenance of clinical and endoscopic remission between the three groups.

**9.2** **Interim Analysis**

An interim analysis of safety data will occur once 50% of randomised participants have completed the studyT

**9.3 Sample size justification**

The study is designed and statistically powered based on the best available data. Study endpoints will be assessed using “intention to treat” (ITT) analysis; however “per protocol” analysis will also be performed. The study is to be powered such that there is a > 80% probability of demonstrating a difference with a p value of 0.05 using a two tailed t-test.

The predicted vedolizumab trough levels based on available data [7,8] are:

* Thiopurine-withdrawal: 5.2 μg/mL
* Thiopurine-continue: 8.8 μg/mL

Power analysis: assuming a standard deviation of 4.5 μg/mL, and enrolling patients in a 2:1 ratio, the study would require 39 patients in the thiopurine-withdrawal group and 20 patients in the thiopurine-continue group to achieve a power of 80% and a level of significance of 5% (two-sided), for detecting a true difference in the means between the two groups of 3.6 (8.8 – 5.2) μg/mL. To account for drop-outs, an extra 6 (10%) patients will be recruited. Hence a total of 65 patients will be required for the study. There is limited available data on vedolizumab trough levels in combination (thiopurine-ongoing) versus monotherapy (thiopurine-withdrawal) groups, and as such, the predicted levels are based on the latest research and abstracts.

**9.4 Data Safety Monitoring Board**

A DSMB will review interim analysis data to ensure the continuing safety of the participants. After the review, the DMSB will make recommendations regarding the continuation of the study.

1. **ETHICAL AND LEGAL ASPECTS**

**10.1 Good Clinical Research Practice**

The procedure set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigators abide by the principles of the Good Clinical Practice (GCP) guidelines of the Therapeutic Goods Administration (TGA) and the ethical principles laid down in the current revision of the Declaration of Helsinki 2008. The study will also be carried out in keeping with local legal and regulatory requirements.

**10.2 Delegation of Investigator Responsibilities**

The investigator will ensure that all persons assisting with the trial are adequately informed about the protocol, the study treatments, and their trial-related duties and functions.

The investigator will maintain a list of co-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

* 1. **Participant Information and Informed Consent**

Before being enrolled in the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the trial have been explained in a form understandable to him or her.

An informed consent document that includes both information about the study and the consent form will be given to the participant. This document will contain all locally required elements and requirements. The document must be in a language understandable to the participant and must specify who informed the participant.

After reading the informed consent document, the participant must give consent in writing. The participants consent must be confirmed at the time of consent by the personally dated signatures of the participant and the person conducting the informed consent discussions.

Patients will be given sufficient time to consider the study (and if relevant, discussion with family and/or primary care physician) prior to written consent being obtained. Copies of the Information Sheet and signed Consent Form will be given to the participant.

It is recommended that the investigator inform the participant’s primary physician about the participation in the trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.

Participants have the right to withdraw from the trial at any time for any reason.

**10.4 Data transcription**

All information required by the protocol must be supplied and an explanation must be given for every missing entry. These data will be entered in the electronic case report form as soon as they are obtained. They will be neatly and legibly written with a black ball-point pen (in order to make duplication and computerization easier) in the source documents. Electronic hospital files will also be accepted if made available for monitoring. Each finished case report form will be dated and signed by the investigator, certifying hereby his/her agreement with reported data. As the study goes along, the case report form will be reviewed by the clinical research assistant, who will review each correct entry and assess data validation.

* 1. **Confidentiality**

Personal data recorded on all study documents will be regarded as confidential. Access to study documents/records of patients will be limited to study investigators and approved study personnel. Study findings stored on a computer will be stored in accordance with local data protection laws. Participants will be told that representatives of the HREC or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a participant identification list (participant numbers with the corresponding participant names, addresses and hospital numbers) to enable patients and their records to be identified. The Investigator will keep these documents in strict confidence in a secure area.

Study investigators will maintain the confidentiality of all patient data and will not reproduce or disclose any information that could identify patients. Participants should be reassured that their confidentiality will be respected at all times.

* 1. **Storage**

The data concerning the study will be stored for 15 years after the end of the study by the investigator.

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10. **APPENDICES**

**APPENDIX 1: Mayo Scoring System**



**Appendix 2: VIEWS Sample Collection and Processing**

|  |  |  |
| --- | --- | --- |
| **Sample** | **Processing** | **Storage**  |
| ***Blood tests*** FBC, EUC, LFT,ESR, CRP | As per local hospital procedures |  |
| ***Blood tests*** 6TGN & 6MMP levels | As per local hospital procedures |  |
| ***Blood tests*** Vedolizumab 3- Concentration- Anti-Vedolizumab Ab | Collect in 2 SST tubes* Ensure thorough clotting
* After spinning, aliquot 0.5ml into at least 4 tubes
* Polypropylene screw top tubes used
 | FROZEN (-70 or 80°C)* 2 tubes for testing
	+ 1 PK, 1 AVA
* 2 back up tubes
	+ 1 PK, 1 AVA
 |
| ***Stool test***Faecal Calprotectin | Use QML pre filled Pathology form with Prof Leong’s information Local Stool collection pot used for sample then frozen and shipped to QML- costs charged to Prof Leong at CRGH | FROZEN |