Investigator Initiated Sponsored Research (IISR) Protocol Guide for Clinical Studies

IISR is defined as unsolicited, independent research where the investigator or the institution (academic, private, or governmental) serves as the Sponsor and Takeda provides support in the form of study drug and/or funding.

IISR proposals are reviewed by Takeda medical and scientific personnel. Decisions are based upon scientific merit as well as alignment with research areas of interest and availability of resources.

Support for an IISR is awarded strictly based on research merit criteria. Support of a study in no way implies any obligation toward or is any way connected to the recommendation or prescribing of Takeda products.

THIS IS AN INSTRUCTIONAL PAGE FOR THE PROTOCOL GUIDE PLEASE REMOVE PRIOR TO SUBMITTING

Black text = Mandatory text. Please do not delete nor edit.
Blue text = Instructions/guide. Please update with study specific information.
Items marked <> need to have the specified item added
Items marked { } give options for recommended/required text

Information to be included with the protocol submission:

General information: • Requestor information (name, email, phone) • Investigator information (name, institution email, phone, institution, address, CV) • Country(s) where study will be conducted • Product(s) • Study title • Study duration (number months, estimated start and end dates – inclusive of projected enrollment) • Resources requested (study drug and/or funding) • Study Type (i.e. clinical interventional, non-interventional, observational)	**Protocol content:** • Background & rationale • Study objectives • Inclusion/exclusion criteria • Study design/schedule (including # of subjects and sites, treatments/procedures) • Study drug • Study endpoints • Study duration • Safety reporting plan • Statistical analysis plan • Data management plan • Publication plan • References • Detailed budget

IISR submissions can be made via the web at www.takeda.com/research/iisr

IISR GUIDE (to be completed in English) STUDY INFORMATION Date: 16/06/2017 Protocol Version: 3	
Country(s) the study will be conducted in:	Australia
Compound/Product: <Generic Drug Name>	Vedolizumab
Study Type : {ie, clinical interventional, clinical non-interventional, observational}	Clinical intervention
Study Title:	Vedolizumab Immunomodulator Enforced Withdrawal Study (VIEWS)
Indication: *List therapeutic area: {Gastroenterology, Diabetes/Metabolism, Hypertension, Central Nervous System, Respiratory, Other}*	Gastroenterology

INVESTIGATOR CONTACT INFORMATION	
Number of Sites: ***(if there are sites multiple countries, name each country and number of sites in each country)***	3 sites in Sydney, Australia
Principal Investigator Contact:	
Principal Investigator Name	Professor Rupert Leong
Organization Name	Concord Repatriation General Hospital
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Telephone	(61) 02 97676111
Fax	(61) 02 97676767
E-mail address	Rupert.leong@health.nsw.gov.au
Co or Sub-Investigator(s) Contact (if applicable):	
Sub-Principal Investigator Name	Dr Webber Chan
Organization Name	Concord Repatriation General Hospital
Address	Level 1 West, ACE unit. Hosptial

	Road,Concord, NSW 2139
Telephone *Fax* *E-mail address*	(61) 02 97676111 (61) 02 97676767 Webber.chan.p.w@singhealth.com.sg
Study Assistant(s)/Coordinator(s) Contact: *Name* *(address, phone number, email)*	Melissa Kermeen (61) 02 97676111 Melissa.kermeen@sswahs.nsw.gov.au
Institution's Contracts or Grants office contact: *Name* *(address, phone number, email)*	-
Name and contact information of person completing this form: *(name, address, phone number, email)*	*Prof Rupert Leong* *Concord Repatriation General Hospital* *Level 1 West, ACE unit. Hosptial Road,Concord, NSW 2139* *(61) 02 97676111* Rupert.leong@sswahs.nsw.gov.au

RESOURCES REQUESTED	
Resource Requested: *{Drug, funding or drug & funding}*	Funding
Estimated Study Budget: *(Enter total here – including direct, indirect cost and institutional overhead)*	$ 359,987.48
Do you have additional funding sources for this project? *(If yes, please explain)*	Yes from. Prof. Rupert Leong's research fund
Dosage and Formulation:	Vedolizumab 300 mg every 8 weekly
Estimated Total Drug Supply for Study: *(number of tablets, capsules, vials)*	Nil; Pharmaceutical Benefits Scheme (Australia) supplied
Total # of Subjects:	78

Study Timeline: *Planned Study Activation: (month/year)* *Study activation is final regulatory authority approved protocol and fully executed contract*	*upon approval of protocol*
Study Activation to First Patient In (days, weeks, months):	*2 months*
First Patient In to Last Patient In *(days, weeks, months)*	*16 months*
Last Patient In to Last Patient Out (days,weeks, months)	*48 weeks*
Monthly enrollment rate: (days)	*6 subjects per month*
Treatment duration: (in months)	*48 weeks*
Number of Study Sites/Depots: (depots are defined as shipment facilities for sites)	*3*
Completion of Data Analysis: (# months)	*3*
Completion of Final Study Report/Manuscript: (month/year)	*May 2020*
Publication Plan: (target journal, target conference)	*Gastroenterology / Clinical gastroenterology and hepatology/ Journal of Crohns'and colitis*

STUDY PROPOSAL

Background:

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic incurable inflammatory disorders of the gastrointestinal tract that cause a global health burden. A major advance in the management was the development of biological therapies to treat IBD. This class of drugs, in the form of monoclonal antibodies, target the proinflammatory cytokine tumor necrosis factor (TNF). Several randomised controlled trials (RCT) have shown that infliximab, adalimumab, certolizumab pegol are efficacious in inducing and maintaining clinical remission in moderate-to-severe Crohn's disease, and for ulcerative colitis, infliximab, adalimumab, and golimumab are effective in inducing and maintaining clinical remission in patients with moderate-to-severe disease activity in whom conventional therapy has failed. Despite the high effectiveness, rates of primary non-response to TNF-α inhibitors in RCTs range between 20 and 40%. Moreover, up to 40% of patients initially responding to TNF-α inhibitors develop intolerable side-effects or lose response overtime. Thus new treatment strategies are needed.

The concept of leucocyte migration into inflamed intestinal tissue has been the target for the development of new biologic therapies. α4β7-integrin is an adhesion molecule expressed on the surface of gut-specific lymphocytes; by binding to mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) on intestinal venules it plays a critical role in the mediation of leukocyte trafficking to the gut. Vedolizumab selectively binds to the α4β7 integrin. The efficacy and safety of vedolizumab in UC and CD has been demonstrated in three pivotal phase III RCTs (GEMINI 1, GEMINI 2 and GEMINI 3) evaluating patients with moderate-to-severe UC or CD who had previously failed at least one prior therapy (e.g. corticosteroids, immunomodulators, TNF-α inhibitors).

The combination of an immunosuppressive agent (e.g. azathioprine or its metabolite, 6-mercaptopurine) with TNF-α inhibitors has proven to be more effective than monotherapy with an immunosuppressive agent or monotherapy with the TNF-α inhibitors. The main role of concomitant immunosuppressive agents is to suppress antibody formation to biological therapies and maintain adequate circulating drug levels. Because of concerns on adverse effects (infections, skin cancers and lymphomas), safety and costs of combination therapy, clinicians always consider withdrawal of therapy once remission is achieved. A recent systematic review on de-escalation of an immunomodulator from combination therapy in IBD showed that in patients discontinued an immunomodulator after combination therapy in CD the rates of relapse did not differ from those of patients who continued taking the drug (55%–60% had disease relapse 24 months after they stopped taking the immunomodulator). The only study in patients with ulcerative colitis supported continued immunomodulator use. Although no difference in efficacy between vedolizumab monotherapy and combination therapy was identified in the GEMINI studies, there is lack of data on the effect of immunomodulator withdrawal after 6 months of combination therapy on vedolizumab trough level and titres of vedolizumab antibodies.

Rationale:

The study is a multicenter, prospective, randomised, single blind trial. The aim of our study is to determine the effects of thiopurine immunomodulator therapy on vedolizumab trough levels and serum C reactive protein levels. To demonstrate this we will measure endpoints in patients randomized to either thiopurine-continuation, thiopurine half-dosing, and thiopurine-withdrawal.

Hypothesis:

That thiopurine withdrawal after ≥6 months of combination therapy with vedolizumab in ulcerative colitis subjects in clinical steroid-free remission does not decrease vedolizumab trough level or raise C-reactive protein levels or titres of vedolizumab antibodies.

Primary Aim/Objective:

For clinical studies– eg, To evaluate the safety and efficacy of interventions with test medication on symptoms, signs and quality of life in patients with target condition.

Primary objective is the median vedolizumab and median CRP levels in the thiopurine-continuation group versus thiopurine-withdrawal group after the 6th infusion post-randomisation (48 weeks)

Secondary Aim/Objective: *(if applicable)*

To determine the effects of thiopurine immunomodulator on vedolizumab levels according to the 3 groups of thiopurine-continuation, thiopurine half-dosing, and thiopurine withdrawal.

To determine if clinical disease activity, need to treatment escalate, CRP, faecal calprotectin and Mayo endoscopic subscore is changed baseline to end-of-study (approx. 48 weeks after randomisation) 3 groups of thiopurine-continuation, thiopurine half-dosing, and thiopurine withdrawal.

To determine whether CRP and vedolizumab levels correlate with thioguanine nucleotide (TGN) levels (per protocol analysis). The thiopurine half-dose group will servce as an exploratory arm to permit for this analysis.

Primary Endpoint(s):

Primary end point is the median CRP and median vedolizumab levels in the thiopurine-withdrawal group versus the thiopurine-continuation group.

Secondary Endpoint(s): *(if applicable)*

- *Clinical relapse between the two groups (defined as Mayo score >2)*
- *Need for treatment escalation with commencement of mesalazine (oral or topical), dose increase of vedolizumab, commencement of corticosteroids (oral or topical) or surgical bowel resection.*
- *Per-protocol median CRP and vedolizumab levels in comparison with TGN levels to determine the effects of immunomodulator on vedolizumab levels in the thiopurine-withdrawal group versus the thiopurine-continuation group versus the thiopurine half-dose group.*
- *The difference in CRP, faecal calprotectin and Mayo endoscopic subscore between these groups and between baseline and 48 weeks.*

Study Plan:

The study is designed as a multicenter, prospective, randomised, single blind trial.

The study will be analysed according to intention-to-treat according to the thiopurine dose group based on randomized allocation.

- *Selection of study population*
- *Ulcerative colitis with steroid free remission for at least 6 months on stable combination therapy with vedolizumab and on optimised thiopurine-immunomodulator for at least 6 months.*
- *Source of recruitment*
- *Patients are recruited from participating IBD-centers in Sydney, Australia including Concord Repatriation General Hospital, Blacktown Hospital and Royal Prince Alfred Hospital.*

Inclusion criteria To be eligible all of the following criteria must be met:

- *Diagnosis of ulcerative colitis.*
- *Male or female, age ≥ 18 years.*
- *Currently treated with a combination therapy with vedolizumab and dose-optimised thiopurine immunomodulators for ulcerative colitis for at least 6 months*
- *Scheduled administration of vedolizumab 300 mg every 8 weeks over the last 6 months.*
- *Appropriate dose of immunomodulators is defined for azathioprine as a maintenance dose of 2–2.5 mg/kg/day or the maximally tolerated dose, or 6 TGN level within therapeutic range; for 6-mercaptopurine as a maintenance dose of 1-1.5 mg/kg/day or the maximally tolerated dose, or TGN level within therapeutic range (235-450 pmol/8 x 10^8 red blood cells)*
- *Patients in steroid free clinical remission for at least 6 months according to clinical assessment*
- *Mayo score 0 or 1 at baseline or recent past.*
- *Use of contraceptive during the whole study for childbearing potential female patients.*
- *Patients able to understand the information provided to them in English and to give written informed consent for the study*

- *Exclusion criteria*
- *Patients who have presented a severe acute or delayed reaction to vedolizumab.*
- *Active perianal/abdominal fistulae at time of inclusion, defined by active drainage*
- *Patients with prior colectomy, ostomy or ileoanal pouch or expected to need surgery*

- *Irresectable colorectal dysplasia, history of colorectal cancer or a non-skin cancer (except for cured-cervical cancer)*
- *Pregnancy, breast-feeding or planned pregnancy during the study*
- *Inability to follow study procedures as judged by the investigator*
- *Non-compliant subjects.*
- *Participation in another therapeutic study*
- *Steroid use within 6 months of screening*
- *Currently receiving steroids, non-thiopurine immunomodulators (such as cycloporin, tacrolimus, methotrexate), biological agent treatment (other than vedolizumab), thalidomide, or experimental clinical trial drug (within 5 half-lives of that drug)*

- *<u>Concomitant medications</u>*

  Permitted medications
- *All medications for ulcerative colitis wapart from vedolizumab and thiopurine immunomodulators according to study design, should remain at stable dosage during the study.*

  Prohibited medications
- *Steroids are not permitted for the last 6 months before entering the study and are not permitted for ulcerative colitis during the study period. Vedolizumab and immunmodulators will be used according to protocol.*
  - *(corticosteroids include budesonide)*

Study Drug(s):

There are 3 treatment arms:

Thiopurine-continuation arm: continuing scheduled vedolizumab treatment and immunomodulators at the same dosage. In case of relapse, the patient will be treated according to investigator's choice.

Thiopurine-withdrawal arm: continuing scheduled vedolizumab treatment and immediately discontinuing immunomodulators on randomisation. If a relapse occurs, the patient will be treated according to investigator's choice.

Thiopurine half-dose arm: continuing scheduled vedolizumab treatment and half of the original dose of concomitant immunomodulators. If a relapse occurs, the patient will be treated according to investigator's choice. This is an exploratory arm to determine a dose-response of thiopurine with vedolizumab trough level.

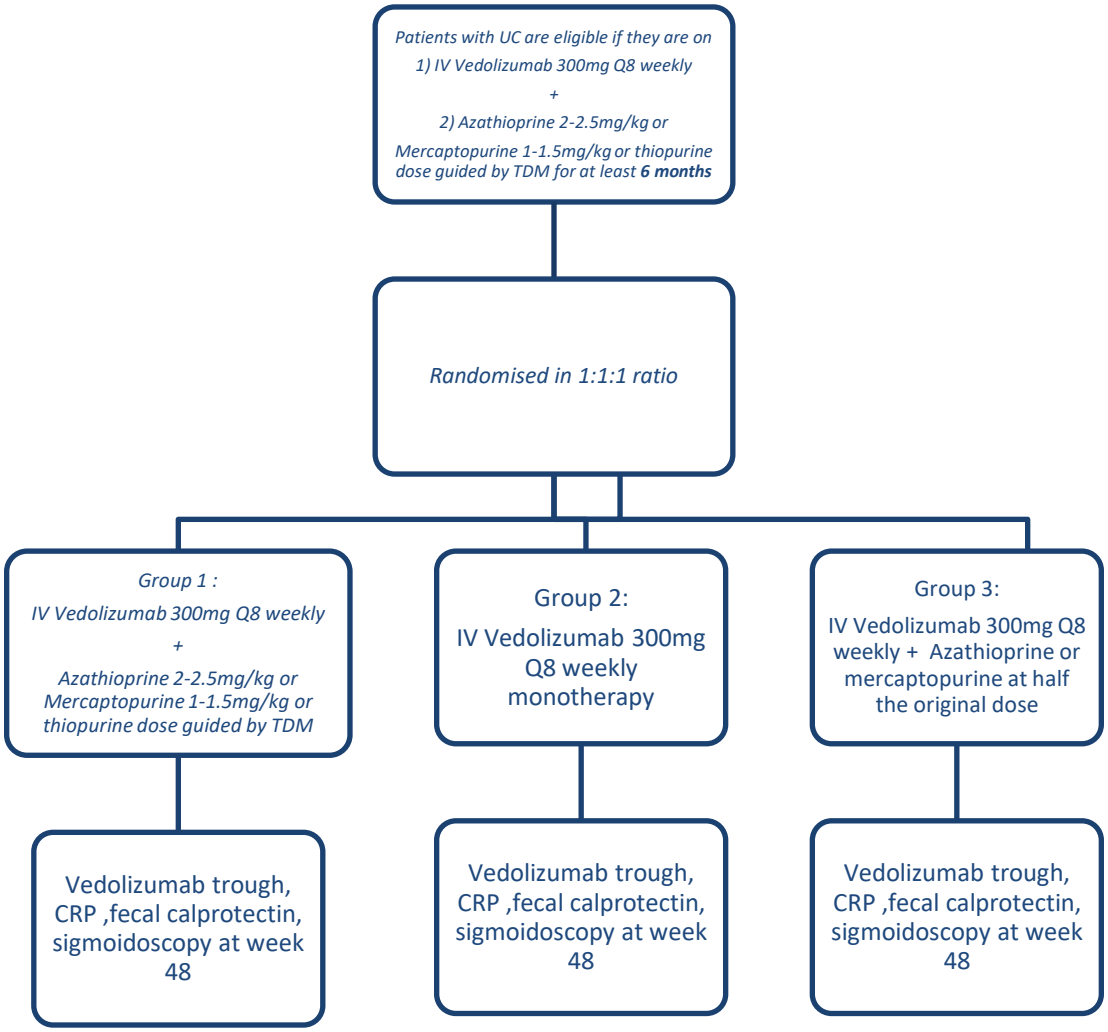
A total of 78 patients will be enrolled in the trial.

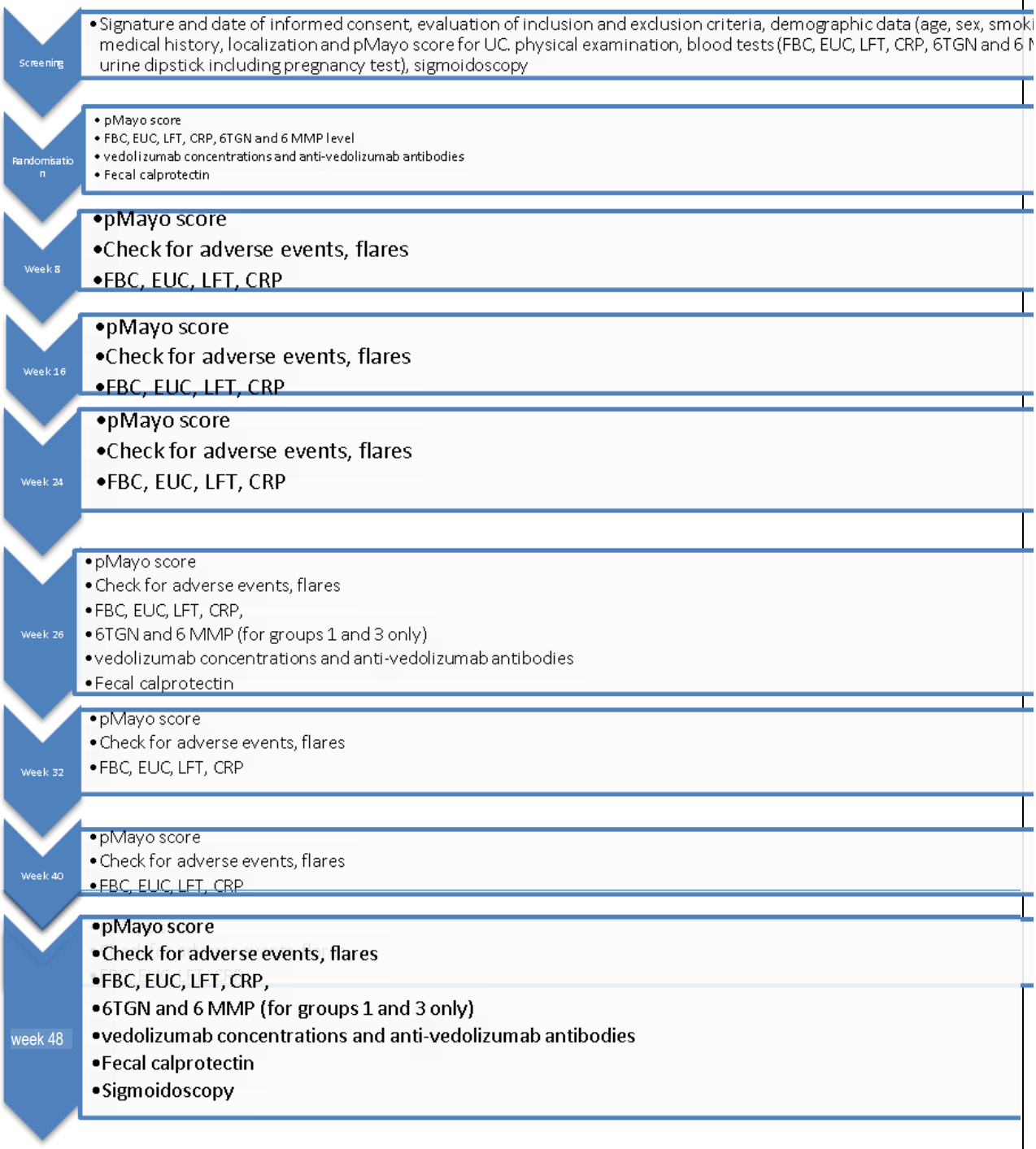
Expected duration and sequence of all study periods, including follow-up. 2 years

Timing of the first dose : upon study activation

Number of visits (or telephone interviews), whether inpatient or outpatient, and other scheduled visits (laboratory tests between visits) : 10

Include supporting tables, graphs and schematics.





Safety Reporting (please do not change the safety section of the template)

Institution/Investigator is solely responsible for reporting all Adverse Events and Serious Adverse Events to regulatory authorities, investigators, IRBs or IECs and Takeda, as applicable, in accordance with national regulations in the countries where the study is

conducted.

Regardless of expectedness or causality, all SAEs and pregnancy reports must also be reported in English by facsimile to Takeda Pharmacovigilance or designee:

> ***Fatal and Life Threatening SAEs*** *within 24 hours of the sponsor-investigator's observation or awareness of the event*
>
> ***All other serious (non-fatal/non life threatening) events*** *within 4 calendar days of the sponsor-investigator's observation or awareness of the event*

<u>Takeda Safety Reporting Contact Information</u>

Takeda requires that all information be communicated to Takeda's Pharmacovigilance Department as outlined in the study contract.

All reported adverse drug reactions and safety issues related to Takeda compound must be included in the final study report.

Describe procedures for reporting Adverse Events and Serious Adverse Events.

Definitions:

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure.*

** This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.*

Serious AE (SAE) means any untoward medical occurrence that at any dose:

1) *results in **death**,*
2) *is **life-threatening**,*

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

3) *requires inpatient* ***hospitalization or prolongation of present hospitalization****,*
4) *results in* ***persistent or significant disability/incapacity****,*
5) *leads to a* ***congenital anomaly/birth defect****,*
6) *may require intervention to prevent one of 1)-5) above or may expose the patient to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.*

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee will request this information from the sponsor-investigator. Please refer to study contract for Takeda pharmacovigilance contact information.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome. Please refer to study contract for Takeda pharmacovigilance contact information.

Product Complaints and Medication Errors

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda and report the event.

A medication error is a preventable event that involves an identifiable patient and that

leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

Phone: 1-877-TAKEDA7 (1-877-825-3327)

E-mail: medicalinformation@tpna.com

FAX: 1-800-247-8860

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance.

Statistical Analysis:

Study Design/Description - The study is a multicenter, prospective, randomised, single blinded trial recruiting ulcerative colitis patients in sustained steroid-free clinical remission who are taking vedolizumab and thiopurine therapy for at least 6 months.

Primary analyses will be according to intention-to-treat

Randomization/Stratification – All patients will continue on vedolizumab 300mg IV every 8 weeks (funded by the Pharmaceutical Benefit Scheme of Australia). The 3 parallel randomised arms are thiopurine-continuation, thiopurine-half dose and thiopurine withdrawal.

Accrual and Feasibility - Provide planned sample size and accrual rate (eg, participants/month). 6-10 subjects per month

Sample size justification: Sample size calculation was based on proportional analysis of vedolizumab trough levels of 1.65 in the thiopurine-withdrawal group versus 2.87 in the thiopurine-continuation group. Standard deviation was calculated as three-quarters of the interquartile range (3.68-1.65=1.5225). Therefore 26 subjects each are required in the thiopurine-continuation arm and the thiopurine-withdrawal arm (total of 52). An exploratory arm will be recruited to determine whether a trough level-response trend can be demonstrated using half-dose thiopurines, but is not subjected to the sample size calculation. To account for potential drop out, non-adherence to treatment, we aimed for a a total of 78 patients to be enrolled in the trial.

Efficacy Analysis.

Analysis will be based on an intention-to-treat basis, that is, based on all included patients whatever the treatment actually received.

One year relapse rates will be estimated by the Kaplan Meier method, then compared between randomised arms between log-rank test. Estimation of the treatment effect will be based on the estimation of hazard ratio (HR), with 95% confidence interval, adjusted on prognostic factors selected by the literature or the data analysis.

Statistical analyses will be performed on SPSS package.

Data Management Plan:

Study Design/Description - The study is a multicenter, prospective, randomised, single blinded trial recruiting ulcerative colitis patients in sustained steroid-free clinical remission who are taking vedolizumab and thiopurine therapy for at least 6 months.

Inclusion Criteria

- *Diagnosis of ulcerative colitis.*

- *Male or female, age > 18 years.*
- *Currently treated with a combination therapy with vedolizumab and immunomodulators for ulcerative colitis for at least 6 months*
- *Scheduled administration of vedolizumab 300 mg every 8 weeks over the last 6 months.*
- *Appropriate dose of immunomodulators is defined for azathioprine as a maintenance dose of 2–2.5 mg/kg/day or the maximally tolerated dose, or 6 TGN level within therapeutic range; for 6-mercaptopurine as a maintenance dose of 1-1.5 mg/kg/day or the maximally tolerated dose, or 6 TGN level within therapeutic range*
- *Patients in steroid free clinical remission for at least 6 months according to retrospective assessment of the patients' files.*
- *Mayo score 0 or 1 at baseline or in recent 12 months.*
- *A contraceptive during the whole study for childbearing potential female patients.*
- *Patients able to understand the information provided to them in English and to give written informed consent for the study*

- *<u>Exclusion criteria</u>*
- *Patients who have presented a severe acute or delayed reaction to vedolizumab.*
- *Active perianal/abdominal fistulae at time of inclusion, defined by active drainage*
- *Patients with ostomy or ileoanal pouch*
- *Pregnancy or planned pregnancy during the study*
- *Inability to follow study procedures as judged by the investigator*
- *Non-compliant subjects.*
- *Participation in another therapeutic study*
- *Steroid use ≤6 months prior to screening*
- *Currently receiving steroids, immunomodulators (other than thiopurine), biologic treatment (other than vedolizumab) or thalidomide*

Ethics approval: in submission

Randomisation: single-blinded as primary outcome is based on objective vedolizumab trough levels. Patients will be aware of thiopurine dose.

Blinding and concealment: based on standard random number generator and randomization concealed in opaque evelope. Block randomization of 8 per series at the three recruitment sites.

Ethical and Regulatory Considerations:

Prior to initiating the study, the Investigator must obtain written approval to conduct the study from appropriate institutional ethical and/or regulatory committee and send a copy to Takeda (gma.externalresearch@takeda.com). Should changes to the study become necessary, copies of written approvals from appropriate institutional ethical and/or regulatory committees must be sent to Takeda (gma.externalresearch@takeda.com).

If research involves human subjects, the Investigator must register the study with clinical trials.gov and other appropriate entities, as necessary.

An IND or CTA may be required. The investigator is responsible to work with regulatory authority to obtain or prove exemption

References:

Torres J et al. Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients With Inflammatory Bowel Disease. Gastroenterology. 2015 Dec;149(7):1716-30.

Feagan BG et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013 Aug 22;369(8):699-710.

Sandborn WJ et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013 Aug 22;369(8):711-21

Supporting documentation/tables and graphs:

Please ensure any supporting tables and graphs are also provided with protocol submission.

Detailed Budget for all study related costs:

Please refer to the budget template accompanied with the notification letter from Takeda and include with your protocol submission.