CLINICAL STUDY REPORT
FAVOUR

Investigation of the Faecal loss of Vedolizumab and its role in influencing serum drug levels, Outcomes and Response in ulcerative colitis

Protocol Short Title/Acronym: FAVOUR

Trial Identifiers

EudraCT Number - **2018-002794-21**

IRAS Number - **210880**

REC Number - **18/LO/1531**

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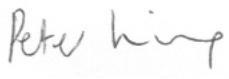
SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

This was a non-commercial academic trial, the results of this study are not intended to be used or a licensing application.

Chief Investigator:

Printed name	**Signature**	**Date**
Peter Irving		1/11/2025

1. Ethics

Independent Ethics Committee or Institutional Review Board

The study protocol and amendments were reviewed and approved by a National Research Ethics Service (London - Westminster).

Ethical conduct of the study

The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent

Patients were identified from routine clinical care. All patients provided informed consent.

Potential participants could be identified by any member of the multidisciplinary direct care team, including registrars, clinical research fellows, consultants as well as clinical nurse specialist and IBD research nurses or pharmacists. Potential participants could be identified during gastroenterology out patient clinics, at endoscopy or during our multidisciplinary meeting ("Virtual Biologics and Immunosuppressant Clinic, VBIC").

The decision to commence vedolizumab treatment will be made in the patients' best interest along standardised clinical treatment algorithms which are in accordance with NICE guidance. Once this decision has been made potential inclusion in FAVOUR will be considered. Patients meeting the inclusion criteria will be invited to take part in the study by a study investigator.

2. Data Monitoring

There was no data monitoring committee or trial steering group for this study.

Glossary of Terms

ADA	Anti-drug antibodies
CRP	C-reactive protein
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
IBD-Q	Inflammatory Bowel Disease Questionnaire; used to assess quality of life in IBD patients
PK	Pharmacokinetics
QoL	Quality of Life
RCT	Randomized controlled trial
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
SCCAI	Simple Clinical Colitis Activity Index
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumor necrosis factor
UC	Ulcerative Colitis

3. Study Synopsis

Title of clinical trial	Investigation of the **Fa**ecal loss of **V**edolizumab and its role in influencing serum drug levels, **Ou**tcomes and **R**esponse in ulcerative colitis
Protocol Short Title/Acronym	FAVOUR
Trial Phase if not mentioned in title	Phase IV
Sponsor name	Guy's & St Thomas' NHS Foundation Trust
Chief Investigator	Peter Irving
Eudract number	2018-002794-21
REC number	18/LO/1531
Medical condition or disease under investigation	Ulcerative colitis (UC)
Purpose of clinical trial	To study the loss of vedolizumab in stool in patients with active UC.
Primary objective	To determine whether vedolizumab is present in significant quantities in the stool of patients receiving induction therapy with vedolizumab for active UC.
Secondary objective (s)	To evaluate whether the presence and quantity of vedolizumab in stool can be used to predict primary non-response to vedolizumab. To explore whether a correlation exists between stool vedolizumab concentrations, serum

	vedolizumab concentrations and UC disease activity and extent. To determine whether there is a correlation between stool and serum vedolizumab levels and trafficking of Th1/Th17 effector memory $CD4^+$ T-cells (the key pathogenic subset in IBD) to the colon in UC.
Trial Design	Prospective, open-label, non-randomised, phase IV trial.
Endpoints	Primary Endpoint: Identification and quantification of vedolizumab loss in faecal samples of patients with active UC. Following this, the correlation between faecal and serum vedolizumab concentrations will be evaluated. Secondary Endpoints: Assessment of the impact of faecal vedolizumab concentrations on rates of clinical and endoscopic response to induction therapy with vedolizumab. Exploratory Endpoints: The correlation between faecal concentrations of vedolizumab and calprotectin will be explored, in addition to the relationship between serum concentration, $CD4^+$ T-cell trafficking and outcomes.
Sample Size	36

Summary of eligibility criteria	Patients with moderate-to-severely active UC who are commencing standard induction therapy with vedolizumab will be prospectively recruited. Inclusion criteria: 1) Aged 18 years or over 2) Written informed consent to participate 3) Simple Clinical Colitis Activity Index > 5 at the time of recruitment to the study, plus one of the following evaluated within 6 weeks of study enrolment***:*** a) A raised fecal calprotectin (> 59 µg/g) ***or****,* b) A raised CRP (> 5 mg/L) ***or****,* c) Endoscopic disease activity ≥ Mayo 2 4) Commencing vedolizumab treatment 5) Sufficient English language skills to understand the patient information sheet and consent form Exclusion criteria: • Contra-indication to vedolizumab (i.e. known serious or severe hypersensitivity reaction to vedolizumab or any of its excipients) • Imminent need for colectomy (i.e. colectomy is being planned) • Previous ileoanal pouch formation • Active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections

IMP, dosage and route of administration	Vedolizumab will be administered in the standard manner, with 300mg intravenous infusions at weeks 0, 2, 6 and 8 weekly thereafter (as is standard of care). Our study will include data collected during the first 14 weeks (4 infusions).
Active comparator product(s)	N/A
Maximum duration of treatment of a Subject	Total duration of treatment will be decided by the supervising physician on clinical grounds (exactly as the standard of care) and enrolment into the study will have no bearing on this decision.

4. Publication (reference)

Manuscript publication in Journal of Crohn's & Colitis:
Samaan MA, Cunningham G, Lim SH, Dawson P, Kottoor SH, Bheekhun Z, Lee E, Anderson SH, Mawdsley J, Ray S, Powell N, Rawstron K, Dart R, Zehra A, Irving PM. Fecal loss of vedolizumab is associated with ulcerative colitis severity, lower serum vedolizumab levels, and rates of clinical response: results from the FAVOUR study. J Crohns Colitis. 2025 Sep 28;19(9):jjaf159. doi: 10.1093/ecco-jcc/jjaf159. PMID: 40891876.

Published in abstract form at the following conferences:

European Crohn's & Colitis Organisation (ECCO) 2024

M Samaan, G Cunningham, S Lim, P Dawson, S H Kottoor, Z Bheekhun, S Anderson, J Mawdsley, S Ray, N Powell, R Dart, K Rawstron, Z Arkir, P M Irving, FAVOUR (Investigation of the Faecal loss of Vedolizumab and its role in influencing serum drug levels Outcomes and Response in ulcerative colitis), P1014 Faecal loss of vedolizumab is associated with UC severity, lower serum vedolizumab levels and rates of clinical response – Results from the FAVOUR study, *Journal of Crohn's and Colitis*, Volume 18, Issue Supplement_1, January 2024, Pages i1833–i1834

British Society of Gastroenterology 2024
Samaan M, Cunningham G, Lim S*, et al*
P108 Faecal loss of vedolizumab is associated with UC severity, lower serum vedolizumab levels and rates of clinical response
Gut 2024;**73:**A115-A116.

US Digestive Diseases Week 2024
Su1817 FAECAL LOSS OF VEDOLIZUMAB IS ASSOCIATED WITH UC SEVERITY, LOWER SERUM VEDOLIZUMAB LEVELS AND RATES OF CLINICAL RESPONSE - RESULTS FROM THE FAVOUR STUDY
Samaan, Mark A. et al. Gastroenterology, Volume 166, Issue 5, S-827 - S-828

5. Study period

Recruitment took place between March 2019 and Jun 2022. First patient first visit occurred on 28-Mar-2019 and last patient last visit occurred on 07-Jun-2022. Patient recruitment was completed on 01-Mar-2022

6. Phase of development

FAVOUR was an open-label, non-randomised, Phase IV trial.

7. Objectives

Primary Objective

To determine whether vedolizumab is present in significant quantities in the stool of patients receiving induction therapy with vedolizumab for active UC.

Secondary Objectives

To evaluate whether the presence and quantity of vedolizumab in stool can be used to predict primary non-response to vedolizumab.

To explore whether a correlation exists between stool vedolizumab concentrations, serum vedolizumab concentrations and UC disease activity and extent.

To determine whether there is a correlation between stool and serum vedolizumab levels and trafficking of Th1/Th17 effector memory $CD4^+$ T-cells (the key pathogenic subset in IBD) to the colon in UC.

8. Background and Context

Faecal loss of biologic agents in ulcerative colitis

Ulcerative colitis (UC) is a chronic condition characterised by idiopathic inflammation of the colonic mucosa. The inflammation seen in UC is limited to the superficial mucosal layer and spreads in a continuous pattern, beginning in the rectum and extending proximally to involve variable extents of the colon. It most commonly occurs in adolescents and young adults and can be associated with significant morbidity.

Until the advent of biologic therapies for UC, options for treatment primarily consisted of the stepwise use of mesalazine, corticosteroids and immunomodulators for disease of increasing severity. Mesalazine was used to achieve and maintain remission in mild-to-moderate cases with the addition of corticosteroids for those failing to respond or with severe disease. Patients with colitis refractory to intravenous corticosteroids received ciclosporin or underwent colectomy.

Over the past decade, clinical trials have demonstrated the efficacy of biologic therapies (including anti-TNF agents and vedolizumab, a selective leukocyte adhesion molecule inhibitor) for patients with moderate to severe UC. These agents are now key tools in current treatment algorithms for patients with moderate- to-severe UC who are refractory to, or intolerant of, conventional treatments. However, a significant proportion of UC patients fail to respond (primary non-response) or lose response over time (secondary non-response).

The investigation of the relationship between monoclonal antibody drug levels and outcomes in inflammatory bowel disease (IBD) is an emerging field. There is a growing understanding of the pharmacokinetics and pharmacodynamics of these agents, as well as an appreciation of their relevance to clinically meaningful endpoints. Whilst proteolysis within the reticuloendothelial system is believed to be the primary route of clearance, it is now understood that multiple other factors are also likely to influence the clearance of monoclonal antibodies. These are thought to include body mass index, gender, use of concomitant immunosuppressive agents, serum albumin concentration and inflammatory burden. In addition to these factors, it has been demonstrated that infliximab is lost into the stool of patients with ulcerative colitis (UC) and that high rates of loss during induction therapy are associated with lower serum concentrations and can predict primary non-response. Successful treatment of active colitis was also observed to be associated with the resolution of this phenomenon. More recently, similar preliminary findings regarding the loss of adalimumab into the stool of patients with colonic ulceration (due to either UC or Crohn's disease) have been reported.

A detailed analysis of serum samples taken during the GEMINI trial program has provided important insights into the pharmacokinetics and pharmacodynamics of vedolizumab. However, this analysis could not account for the impact of faecal vedolizumab losses, as this data was not captured as part of the trial. Despite this, based on the findings described above, it appears likely that faecal loss will be an important determinant of serum vedolizumab concentrations as well as response to induction therapy.

Determining whether serum vedolizumab levels (and loss in faeces) correlate with reduced trafficking of pathogenic Th1/Th17 CD4$^+$ T-cells to the colon

Gut homing CD4$^+$ T-cells likely play a central role in UC pathogenesis and are thought to be the major cellular target of vedolizumab therapy. Although there are several different effector subsets (e.g. Th1/Th2/Th17) that exist in different stages of development (naïve, effector memory and central memory), it is the subset of effector memory cells that co-produce interferon-γ and IL17 (so called Th1/Th17 cells) that are thought to be the especially pathogenic and are enriched in the colon of UC patients. We propose that vedolizumab therapy will reduce the number of Th1/Th17 effector memory (EM) CD4$^+$ T-cells recruited to the colon at week 14 (in

comparison with baseline numbers). Furthermore, we will test the hypothesis that UC patients with the highest levels of serum vedolizumab (and lowest levels of faecal loss vedolizumab) will have the most pronounced reduction in Th1/Th17 EM $CD4^+$ T-cell recruitment to the colon. We have designed a comprehensive multiparameter flow cytometry panel (appendix 3) to enumerate the proportion of Th1/Th17 effector memory (EM) $CD4^+$ T-cells in blood and colon at baseline (prior to treatment) and week 14 of treatment (outcome sigmoidoscopy). Interestingly, in keeping with the likely important pathogenic role of the Th1/Th17 subset, our preliminary data indicates that the Th1/Th17 subset has the highest proportion of cells expressing β7.

9. Methodology

Laboratory Samples

Faecal and serum vedolizumab measurements (as well as measurements of antibodies to vedolizumab) will be made using ELISA techniques. Due to the innovative nature of our proposed study no published methodology has yet been described to measure vedolizumab in faeces. The most relevant methodology for the measurement of monoclonal antibodies in faecal samples has been described for an assay of infliximab in faeces. The methods described are as follows:

Faecal samples were diluted 1:5 in phosphate-buffered saline containing 6% bovine serum albumin. Samples were then homogenized by vortexing for 60 minutes, centrifuged at 3000g for 5 minutes, and 100 mL supernatant was collected and stored in freezer (20C). Infliximab concentrations were measured in faecal supernatants using an enzyme linked immunosorbent assay (Sanquin Biologicals Laboratory, Amsterdam, The Netherlands; lower limit of quantitation, 0.03 mg/mL).

In conjunction with our well established reference chemistry laboratory group we plan to adapt this methodology to allow the quantification of vedolizumab in faecal samples.

Serum CRP and albumin will be quantified as well as fecal calprotectin.

Biopsy Samples

Biopsy samples will be taken by the performing endoscopist at the time of flexible sigmoidoscopy. Participants will have been recruited to the study prior to the procedure taking place and as part of that consent process will have had the chance to consider whether donating biopsy samples is acceptable to them. They will also be consented separately by the endoscopy team for the flexible-sigmoidoscopy procedure and biopsy sample acquisition (to be used as part of standard care, rather than research).

Samples will be taken from the most inflamed area in the rectosigmoid region of the colon. They will be treated, transported and stored in accordance with HTA regulations. The pseudonymised samples will be stored in a freezer within the mucosal

immunology laboratory at King's College Hospital (Guy's campus, New Hunts House). A record will be made at the point of collection and upon arrival at the laboratory. None of these samples will be stored beyond the end of the study.

4.1.1 Primary endpoints

Our primary endpoint is the identification and quantification of vedolizumab loss in faecal samples of patients with active UC. Following this, the correlation between faecal and serum vedolizumab concentrations will be evaluated.

4.1.2 Secondary and exploratory endpoints

Assessment of the impact of faecal vedolizumab concentrations on rates of clinical response to induction therapy with vedolizumab. UC disease activity using SCCAI using the following definitions:

Remission	SCCAI ≤ 2
Response	SCCAI ≤ 5, with a decrease by ≥ 2
Relapse	SCCAI ≥ 5 (following a response)

Clinical disease activity will be assessed primarily using SCCAI at baseline, weeks 2, 6 and 14. Clinical response will be defined as an SCCAI < 5, or an SCCAI decrease of ≥ 50% from the baseline value

Endoscopic disease activity will be assessed at flexible sigmoidoscopy at baseline and week 14. Endoscopic response will be defined as improvement of the endoscopic Mayo score of at least 1 point from baseline to week 14[1, 2]. UCEIS scores will also be evaluated as an exploratory outcome[3, 4].

Secondary UC disease activity assessments will be made using PRO2[5], faecal calprotectin, serum CRP and albumin. PRO2 is a recently described patient reported outcome measure for clinical disease activity in UC. It will be scored alongside SCCAI as an exploratory endpoint to assess its utility. It consists of two items: rectal bleeding and stool frequency.

Histological assessments will be made on endoscopic biopsy samples taken at baseline and week 14. The recently developed and internally validated Nancy index will be used to evaluate histological disease activity[6]. The correlation between faecal vedolizumab loss and histological activity will be explored.

Quality of life assessments will be made using: IBD-Control[7].

In addition, the relationship between faecal concentrations of vedolizumab and calprotectin will be explored.

Demographic parameters

Baseline values and parameters, such as: age, gender, concomitant medication, anatomic distribution and duration of disease.

4.2 Trial Design

This will be an open-label, non-randomised, phase IV trial.

The study will be initiated and primarily run at Guy's and St Thomas' Hospital, a tertiary IBD referral center.

The end of trial will be deemed as date of final database lock and completion of analysis of laboratory samples collected from participants

Trial Flowchart

	Screen Visit	Endoscopy visit (within 6 weeks of screen)	Day 0 (within 6 weeks of endoscopy)	Day 1 (+1 day)	Day 4 (+/- 1 day)	Day 7 (+/- 1 day)				Endoscopy visit (within 6 weeks of week 14 visit)
						Week 1 (+/- 1 day)	Week 2 (+/- 7 days)	Week 6 (+/- 7 days)	Week 14 (+/- 7 days)	
Signed informed consent	**X**									
Collection of demographic and UC disease related data	**X**									

Review inclusion/exclusion criteria	X		X							
IBD-relevant concomitant medication review	X		X				X	X	X	
Vedolizumab administration			X				X	X	X	
Faecal vedolizumab measurement				X	X	X	X	X	X	
Serum vedolizumab and antidrug antibody measurement							X	X	X	
Clinical disease activity scores			X				X	X	X	
Serum CRP and albumin measurement			X				X	X	X	
Faecal calprotectin			X				X	X	X	
Quality of life questionnaire			X				X	X	X	
Flexible-sigmoidoscopy & biopsy		X								X

10. Table 1. Number of patients (planned and analysed)

Arm	Active
# patients screened	40
# patients randomised/treated/ study arm	36
# patients completed/ study arm	32
Reasons for non-completion if applicable	3 patients due to non-response 1 lost to follow-up

Table 2. The reasons for patient withdrawal from the study

Patient	Comments
3 patients	UC non-response
1 patient	Lost to follow-up

11. Diagnosis and main criteria for inclusion

Inclusion Criteria

Adult patients with moderate-to-severe UC with an inadequate response to, or unable to tolerate, one or more of the following conventional therapies: oral 5-aminosalicylates, oral corticosteroids, immunomodulators; or are corticosteroid dependent.

Inclusion criteria definitions:

- Aged 18 years or over, either male or female
- Moderate-to-severe UC, defined as:
    - SCCAI > 5 at the time of recruitment to the study, plus one of the following evaluated within 6 weeks of study enrolment*;,*
        i. A raised fecal calprotectin (> 59 µg/g) *or,*
        ii. A raised CRP (> 5 mg/L) *or,*
        iii. Endoscopic disease activity Mayo 2 or above,
- Commencing vedolizumab treatment
- Sufficient English language skills to understand the patient information sheet and consent form

Exclusion Criteria

- Contra-indication to vedolizumab (i.e. known serious or severe hypersensitivity reaction to vedolizumab or any of its excipients)
- Imminent need for colectomy (i.e. colectomy is being planned)
- Previous ileoanal pouch formation
- Active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections

Selection of Participants

Potential participants could be identified by any member of the multidisciplinary direct care team, including registrars, clinical research fellows, consultants as well as clinical nurse specialist and IBD research nurses or pharmacists. Potential participants could be identified during gastroenterology out patient clinics, at endoscopy or during our multidisciplinary meeting ("Virtual Biologics and Immunosuppressant Clinic, VBIC").

The decision to commence vedolizumab treatment will be made in the patients' best interest along standardised clinical treatment algorithms which are in accordance with NICE guidance. Once this decision has been made potential inclusion in FAVOUR will be considered. Patients meeting the inclusion criteria will be invited to take part in the study by a study investigator.

12. Test product, dose and mode of administration

Investigational Medicinal Product

Vedolizumab (Millennium Pharmaceuticals (a subsidiary of Takeda Pharmaceuticals), Cambridge, Massachusetts, US) is an intravenously administered selective leukocyte adhesion molecule inhibitor.

Dose Regimen

Vedolizumab was administered intravenously at a dose of 300mg at weeks 0, 2, 6 and 14.

IMP Risks

Vedolizumab has been studied in three placebo-controlled clinical trials in patients with ulcerative colitis (GEMINI I) or Crohn's disease (GEMINI II and III). In two controlled studies (GEMINI I and II) involving 1,434 patients receiving vedolizumab 300 mg at Week 0, Week 2 and then every eight weeks or every four weeks for up to 52 weeks, and 297 patients receiving placebo for up to 52 weeks, adverse events were reported in 84% of vedolizumab-treated patients and 78% of placebo-treated patients. Over 52 weeks, 19% of vedolizumab-treated patients experienced serious adverse events compared to 13% of placebo-treated patients. Similar rates of adverse events were seen in the every eight week and every four week dosing groups in the Phase 3 clinical trials. The proportion of patients who discontinued treatment due to adverse events was 9% for vedolizumab-treated patients and 10% for placebo-treated patients. In the combined studies of GEMINI I and II the adverse reactions that occurred in ≥5% were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, cough. Infusion-related reactions were reported in 4% of patients receiving vedolizumab.

Drug Accountability

No accountability as this is part of standard care. As patients are being treated as part of standard care, the IMP will be supplied by the NHS (i.e. not by Takeda).

Storage of IMP

IMP will be stored as per the SmPC requirements as part of standard care. No labelling of the IMP will be required since it is a Type A trial and the study drug will be used from commercial stock and according to its SmPC

Subject Compliance

No specific compliance testing will be carried out but non-compliance could be deduced based on serum drug levels made as part of the trial.

13. Criteria for evaluation: Endpoints

Primary Efficacy Parameters

UC disease activity using SCCAI using the following definitions:

Remission	SCCAI ≤ 2
Response	SCCAI ≤ 5, with a decrease by ≥ 2
Relapse	SCCAI ≥ 5 (following a response)

Secondary Efficacy Parameters

Endoscopic UC disease will be judged using the Mayo score and UCEIS. Clinical disease activity assessments using PRO2, development of anti-drug antibodies, fecal calprotectin, serum CRP measurements, albumin, QoL assessments using IBD-control.

Procedures for Assessing Efficacy Parameters

For serum trough vedolizumab levels, anti-drug antibodies and CRP venepuncture will be carried out with 25 ml of blood to be drawn just prior to the next vedolizumab infusion. This will be done at the time of cannulation so will not pose any additional or discomfort.

Faecal vedolizumab and calprotectin measurements will be made on stool samples.

Clinical disease activity and quality of life measurements will be made at the same visit as the vedolizumab infusions.

Flexible-sigmoidoscopy will be carried out at baseline and after week 14.

Safety

Assessment of Safety

Specification, Timing and Recording of Safety Parameters

General safety assessments will be made as part of each assessment.

Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

Results in death;
Is life-threatening;
Required hospitalisation/prolongation of existing hospitalisation;
Results in persistent or significant disability or incapacity;
Consists of a congenital anomaly or birth defect.

Important Medical Events (IME) & Pregnancy

Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

Reporting Responsibilities

King's Health Partners Clinical Trials Office (KHP-CTO) is responsible for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004.

All SAEs, SARs and SUSARs will be reported immediately by the Chief Investigator (and certainly no later than 24hrs) to the KHP-CTO in accordance with the current Pharmacovigilance Policy.

The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

Adverse events that do not require reporting

Non serious AE's will not be collected during the study period but will be managed as per the standard of care. Infusion reactions listed as expected as per the SmPC will not be reported.

14. Statistical Methods

Continuous data are summarised as medians (or means, where specified) and range (in brackets). Paired SCCAI, CRP and FC values were compared using Wilcoxon signed-rank test. Non-responder imputation was used to manage missing data. Categorical variables were compared using the Fisher's exact or Mann-Whitney U. Correlations between variables were calculated with the Spearman correlation

coefficient (r_s). Area under the curve (AUC) was calculated using the trapezoidal rule and AUC values were compared using unpaired t-test. Analysis of Variance (ANOVA) testing was used to evaluate trends across multiple groups. Analyses were carried out using GraphPad Prism v10.1.1. Unless stated, p values are non-significant with $p<0.05$ being considered statistically significant. All data below/above the limit of quantification were substituted with the value of the lower/upper limit of quantification, i.e. CRP 1mg/L for levels of < 1mg/L, and FC 8000 ug/g for levels > 8000 ug/g.

15. Summary – Conclusions

Table 3. Age and gender

Number of Subjects			
Age (years)	**Male**	**Female**	**Total**
Pre-term new-born infants (<37 weeks)	0	0	0
New-borns (0-27 days)	0	0	0
Infants and toddlers (28 days – 23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	12	32
Elderly (65-84 years)	3	1	4
85 years and over	**0**	**0**	**0**
Total	**23**	**13**	**36**

Table 4. Patient demographics and clinical characteristics

Patient characteristics	n = 36
Gender, male:female, n (%)	23:13 (64:36)
Median age (range), years	35 (18-73)
Median disease duration (range), years	9 (1-50)
Median SCCAI (range)	5 (1-12)
Median Mayo endoscopic score (range)	2 (1-3)
Median UCEIS (range)	5 (2-6)
Median NHI (range)	3 (0-4)
Median faecal calprotectin (range), ug/g	385 (9-8000)
Median albumin (range), g/L	44 (35-51)
Median CRP, mg/L	1 (1-31)
Disease extent, n (%)	
Proctitis	5 (14)
Left-sided	21 (58)
Extensive	10 (28)
Corticosteroids, n (%)	14 (39)
Prior anti-TNF experience, n (%)	
Naïve	19 (53)
Exposed	17 (47)

Ethnicity data was not collected for this study.

Outcome

Patient characteristics

A total of 36 patients commencing vedolizumab induction therapy were recruited; 32 completed the 14-week study protocol. Three patients discontinued treatment between weeks 6 and 14 due to lack of efficacy and one was lost to follow-up. Their data were included in the pharmacokinetic analyses and they were considered week

14 non-responders. Baseline characteristics of the included patients are detailed in table 1. Overall, the patient cohort had moderately active disease when measured clinically (median SCCAI 5), endoscopically (median UCEIS 5) and histologically (median NHI 3). They had a median disease duration of 9 years, just under half had prior anti-TNF exposure (17/36, 47%) and 14/36 (39%) were treated with corticosteroids at baseline (table 1).

Clinical, biochemical, endoscopic and histologic disease activity

The median SCCAI score fell from 5 (1-12) at baseline to 4 (0-12, p=0.052, n=36) at week 2, 3 (0-12, p=0.0007, n=36) at week 6 and 1 (0-12, p<0.0001, n=33) at week 14. Rates of clinical response and remission at week 14 were 26/36 (72%) and 22/36 (61%), respectively.

The median FC fell from 385 ug/g (9-8000) at baseline to 308 ug/g (5-3870, p=0.18, n=33) at week 2, 165 ug/g (6-2270, p=0.24, n=33) at week 6 and 69 ug/g (5-1180, p=0.004, n=31) at week 14. The median CRP was 1 mg/L (1-31) at baseline, 2 mg/L (1-45, p=0.26, n=36) at weeks 2 and week 6 (1-18, 0.73, n=36) and 1 mg/L (1-16, p=0.97, n=32) at week 14.

In addition to the 3 patients who withdrew due to inefficacy, a further 3 declined post-induction endoscopy but continued treatment; non-responder imputation was used for all 6. Endoscopic disease activity improved from a median UCEIS of 5 (2-6) at baseline to 2 (0-6, n=30) at week 14. Corresponding Mayo endoscopic scores were 2 (1-3) and 1 (0-3, n=30), respectively. Using UCEIS thresholds of 0 or 1 for endoscopic remission and a decrease by >2 points for response, rates of 15/36 (42%) and 18/36 (50%) were observed, respectively.

As for endoscopic outcomes, the 6 patients without NHI outcomes at week 14 were considered non-responders. Median NHI fell significantly from 3 (0-4) at baseline to 2 at week 14 (0-4, p=0.006, n=29). The rate of histologic remission was 14/36 (39%).

Quality of life

The median baseline IBD-Control score was 5 (0-14). By week 2, quality of life had improved significantly to a score 10 (2-16, p<0.0001, n=36) and remained

significantly improved at 11 at week 6 (1-16, p<0.0001 vs baseline, n=36) and 14 (0-16, p<0.0001, n=33) at week 14.

Serum vedolizumab levels

Amongst the 36 patients, a total of 104 serum vedolizumab samples were collected across the 3 study timepoints during the 14-week protocol (4 samples were omitted due to protocol deviations or issues with processing).

Faecal vedolizumab levels

A total of 203 faecal vedolizumab samples were collected across the 6 study timepoints during the 14-week protocol (13 samples were omitted due to protocol deviations or issues with processing).

Vedolizumab was detectable, at any level, in 80/203 (39%) of faecal samples (figure 1). Of the 36 patients, 28 (78%) had detectable faecal vedolizumab at some point during the 14-week protocol. Mean faecal vedolizumab levels were 3.9 ug/mL (0.0-64.7 ug/g, n=36 samples) at day 1, 1.6 ug/mL (0.0-21.6, n=35) at day 2, 0.8 ug/mL (0.0-5.8, n=32) at day 7, 0.3 ug/mL (0.1-1.3, n=34) at week 2, 1.9 ug/mL (0.0-49.4, n=35) at week 6 and 0.1 ug/mL (0.0-1.8, n=31) at week 14. Due to the high proportion of faecal samples with no detectable vedolizumab, corresponding median values were 0.2 ug/mL at day 1 and then 0.0 ug/mL at all other timepoints. Of the 36 patients, only 8 (22%) had no detectable faecal vedolizumab at any timepoint.

Relationship between disease activity, treatment outcomes and faecal vedolizumab levels

Statistically significant correlations were observed between FVL and several markers of clinical, biochemical, baseline endoscopic and histologic disease activity at days 1, 4 and 7 as well as weeks 2 and 6 (table 2). There were no statistically significant correlations observed at week 14. The most consistent predictor of faecal vedolizumab loss was baseline UCEIS, with strong associations being observed at days 1, 4, 7 and week 2, and a moderate association at week 6.

Faecal vedolizumab loss was also compared between week 14 responders/remitters and non-responders/remitters at each study timepoint using both clinical and endoscopic definitions of response and remission. The only statistically significant

difference observed was that week 14 clinical non-responders had higher FVL than responders at that timepoint (median 1.0 vs 0.0ug/mL, p=0.0042) but not at any of the preceding timepoints.

Area under the curve (AUC) analysis demonstrated significant differences in cumulative faecal vedolizumab loss between clinical responders and non-responders, as well as between endoscopic responders and non-responders. AUC for week 14 clinical response was 233 ug/mL/day, compared with 44 ug/mL/day for non-response (p<0.0001)(figure 2A). The corresponding value for endoscopic response was 179 ug/mL/day, compared with 48 ug/mL/day for endoscopic non-response (p=0.0017)(figure 2B).

Relationship between faecal vedolizumab levels, serum vedolizumab levels and treatment response

A significant, inverse correlation was observed between day 7 faecal vedolizumab levels and serum levels measured at week 6 (r=-0.42, p=0.02). Inverse correlations were also observed between week 2 faecal levels and serum levels measured at weeks 6 (r=-0.45, p=0.008) and 14 (r=-0.38, p=0.033)(table 2).

Median SVL did not differ significantly between week 14 clinical responders and non-responders at any time point (29 vs 33 ug/ml at week 2 (p=0.33), 33 vs 29 ug/ml at week 6 (p=0.81), 17 vs 16 ug/ml at week 14 (p=0.61), respectively). In addition, AUC analysis did not demonstrate any difference in cumulative exposure between week 14 clinical responders (2223 ug/mL/day) and non-responders (2174 ug/mL/day, p=0.60). However, significant differences were seen at each timepoint when comparing endoscopic responders and non-responders. Median serum levels were 32.9 vs 27.6 ug/ml (p=0.013) at week 2, 35.4 vs 24.3 ug/ml (p=0.0066) at week 6 and 21.5 vs 9.3 ug/ml (p=0.0007) at week 14, respectively. In keeping with this, a significant difference in AUC cumulative exposure was observed between endoscopic responders (2592 ug/mL/day) and non-responders (1818 ug/mL/day, p<0.0001).

Effect of disease extent on faecal vedolizumab loss

Area under the curve analysis was used to compare cumulative rates of faecal vedolizumab in groups divided by disease extent. This demonstrated a statistically significant trend such that patients with proctitis (AUC 42.7 ug/mL/day) had lower cumulative loss than patients with left-sided disease (AUC 62.8 ug/mL/day), who in turn, had lower cumulative rates of loss than patients with extensive disease (AUC 218.5 ug/mL/day, ANOVA p=0.0012 for trend).

Safety results

There were 5 SAE’s amongst 4 patients, all related to worsening of UC and non-considered related to the study drug. Non-serious AE’s were not collected as part of FAVOUR.

Table 5: Listing of Serious Adverse Events for all patients

Serious Adverse Events	e.g. Treatment Arm	e.g. Placebo
Total Number of SAEs per Study Arm	5	N/A
Total number of all cause deaths per Study Arm	0	N/A
Total number of deaths resulting from adverse events per Study Arm	0	N/A

Within the per protocol population (n= 36), a total 5 SAE, were identified as treatment-emergent and included in the safety analysis. Summary tables for SAEs are presented in the appendix of this synopsis. Overall, 4 patients (11%) experienced at least one SAE. Non-serious AE's were not collected as part of FAVOUR.

16. Changes in the Trial Plan

The pre-specified statistical analysis plan was written and approved before the start of the statistical analysis. There were no changes to the planned analysis.

a. Protocol Deviations

No serious breaches or any major protocol deviations occurred and therefore no impact on the analysis.

17. Conclusion

Active UC results in faecal loss of vedolizumab. This correlates with lower SVL and decreased response to treatment. Faecal loss of vedolizumab may be a marker of disease activity and/or result in lower rates of drug exposure at a tissue level, negatively impacting response. The primary objective was met.

18. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 1/11/2025