PROTOCOL FULL TITLE:

Study of the Golimumab Exposure-Response Relationship using Serum Trough Levels

Protocol Short Title/Acronym: GO-LEVEL

Trial Identifiers

EudraCT Number - 2017-001374-42
CRN/CPMS - 34486
IRAS Number - 194917
ClinTrials.gov - NCT03124121

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1. Study Synopsis

Title of clinical trial	Study of the Golimumab Exposure-Response Relationship using Serum Trough Levels
Protocol Short Title/Acronym	GO-LEVEL
Trial Phase if not mentioned in title	Phase IV
Sponsor name	Guy's & St Thomas' NHS Foundation Trust
Chief Investigator	Peter Irving
EudraCT number	2017-001374-42
IRAS number	194917
Medical condition or disease under investigation	Ulcerative colitis (UC)
Purpose of clinical trial	To study the exposure-response relationship of golimumab using serum trough levels
Primary objective	To define a week 6 golimumab trough level concentration that predicts response at week 14
Secondary objective (s)	To define golimumab trough level concentrations at weeks 6, 10 and 14 that predict response at each time point during induction therapy, respectively. To define a golimumab trough threshold that is associated with remission during maintenance therapy. Tertiary objectives will centre on the study of the relationship between serum golimumab trough levels and novel disease activity indices (PRO2), biochemical markers of disease activity (CRP, faecal calprotectin) and quality of life indices. The role of anti-drug antibodies will also be investigated in relation to trough levels and disease activity.

Trial Design	Open-label, non-randomised, phase IV trial. Patients commencing induction therapy with golimumab (cohort 1) will be enrolled into a prospective study. Patients on maintenance golimumab therapy (cohort 2) will be enrolled into a cross-sectional study.
Endpoints	Primary: golimumab trough levels and UC disease activity (SCCAI) at weeks 6 and 10 Secondary: biochemical markers of UC disease activity (fecal calprotectin and CRP), clinical disease activity (PRO2), development of antibodies and quality of life (IBD-Control) at weeks 6, 10 and 14.
Sample Size	Total: 112 patients (cohort 1: 42 patients, cohort 2: 70 patients)
Summary of eligibility criteria	Inclusion criteria for cohort 1: • Aged 18 years or over • Written informed consent to participate • Moderate-to-severe UC, defined as: o SCCAI > 5 *and,* ▪ A raised fecal calprotectin (> 59 µg/g) *or,* ▪ A raised CRP (> 5 mg/L) *or,* ▪ Endoscopic disease activity Mayo 2 or above, ***Evaluated within 4 weeks of screening*** • Commencing golimumab treatment • Sufficient English language skills to understand the patient information sheet and consent form Inclusion criteria for cohort 2: • Aged 18 years or over • Written informed consent to participate • Receiving golimumab treatment for UC over 14 weeks (have completed 6 injections at time of screening) • Sufficient English language skills to understand the patient information sheet and consent form

	Exclusion criteria (cohort 1 only) • Contra-indication to golimumab: tuberculosis, severe infections or congestive cardiac failure • Imminent need for colectomy (i.e. colectomy is being planned) • Previous primary non-response to anti-TNF therapy in the opinion of the investigator • Previous treatment with more than one anti-TNF therapy (excluding golimumab)
IMP, dosage and route of administration	Patients will receive standard induction treatment with subcutaneous golimumab 200 mg at week 0 and 100 mg at week 2. Followed by maintenance treatment of 50 or 100 mg (based on weight) every four weeks until the supervising clinician makes the decision to withdraw treatment (as is the standard of care).
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.
Version and date of protocol amendments	Version 4.1, 13th June 2019

2. 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
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. Background & Rationale

The advent of biologic therapies has led to significant changes in treatment strategies for ulcerative colitis (UC). Prior to biologic therapies, 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 (IV) corticosteroids received ciclosporin or underwent colectomy. Over the past decade, multiple clinical trials have shown the efficacy of anti-TNF therapies for these patients with moderate to severe UC. Therefore, Anti-TNF agents are key tools in current treatment algorithms for both chronically active and acute severe UC.

The effectiveness of biologic agents has also changed treatment goals in ulcerative colitis. This is evident in the evolution of endpoints used for clinical trials and targets used in clinical practice. Conventional and established goals of treatment focused predominantly on achieving symptomatic remission. The cessation of corticosteroid use and achieving mucosal healing were secondary goals. However, in the era of anti-TNF agents with the ability to heal colonic mucosa when other drugs have failed, mucosal healing and steroid-free clinical remission have gained prominence as therapeutic targets.

A significant proportion of UC patients fail to respond to induction therapy with anti-TNF agents (primary non-responders) or require dose escalation due to loss of response over time (secondary non-responders). Dose escalation has been demonstrated to be an effective strategy in patients losing response to anti-TNF therapy. Where this strategy fails or in the presence of significant levels of anti-drug antibodies, switching to another anti-TNF agent (or mechanism of action) is advocated. Therefore, an increase in the range of anti-TNF agents available to clinicians was desired and necessary to overcome the substantial rates of non-response over time. In addition, a better understanding of the effect-response relationship of these agents would allow a more evidence-based approach to dose optimization.

Golimumab represents a new treatment option for patients with moderate-to-severe UC, failing or intolerant of conventional treatments. It is a transgenic, fully human monoclonal immunoglobulin G1 antibody that is synthesized from TNF-immunized transgenic mice expressing human immunoglobulin G. Although it was approved for use in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis in 2009, it was not until 2013 that the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) granted approval for UC.

The PURSUIT (Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment) trial program was a series of randomized, double-blind, placebo-controlled studies that led to regulatory approval for the use of golimumab in UC[1,2]. The comprehensive trial program consisted of investigation of the most appropriate route of administration (subcutaneous or intravenous), a phase II dose-ranging study and a phase III trial of induction and maintenance therapy. Subcutaneous administration was found to result in equivalent efficacy and a preferable pharmacokinetic profile when compared with intravenous dosing and is therefore the approved route of administration. PURSUIT-SC demonstrated that induction therapy with golimumab resulted in a significantly greater proportion of patients achieving a

clinical response, clinical remission and mucosal healing at week 6 compared with placebo[1]. All subjects from the PURSUIT-SC study were eligible for enrollment into PURSUIT-M, which evaluated the efficacy and safety of golimumab maintenance therapy over 54 weeks. On-going treatment with golimumab was shown to result in a significantly increased rate of sustained clinical benefit (both response and remission) compared with placebo[2].

However, despite the fact that the PURSUIT trial program yielded positive results and met its primary endpoints, unanswered questions remain regarding the optimal use of golimumab in UC. For example, how could the observed rates of primary and secondary non-response (approximately 50% and 40%) be minimized? In addition to significant rates of non-response, the majority of patients who do respond to the drug remain symptomatic to some degree, are on concomitant steroids, and are without a “normal or inactive” (Mayo 0) mucosal appearance. It’s possible that these outcomes could be improved upon, given a more detailed understanding of the initial exposure-response relationship data that emerged from PURSUIT.

Patients with higher serum concentrations of golimumab were observed to have higher rates of response and remission as well as greater improvement in median composite Mayo scores. In PURSUIT-SC the change from baseline Mayo score and rates of clinical response and clinical remission at week 6 increased with increasing quartiles of serum golimumab concentration. Serum quartile analysis of the subsequent maintenance trial showed that more patients in the higher quartiles achieved clinical response through to week 54, or clinical remission at both weeks 30 and 54, when compared with those in the lower quartiles.

In a recent publication, Adedokun and colleagues reported a rigorous and meticulously performed a study of the pharmacokinetics and pharmacodynamics of golimumab using samples taken as part of the PURSUIT trials. As part of these analyses the authors found serum golimumab concentrations to be dose proportional and that a positive correlation exists between concentrations and efficacy outcomes (clinical response, clinical remission and mucosal healing) during induction and maintenance therapy. They then went further by using receiver-operating-characteristics (ROC) curve analysis to define serum golimumab concentrations that may serve as potential targets for treatment optimization; proposing thresholds of 2.5 µg/ml at week 6 and 1.4 µg/ml during steady-state maintenance therapy[3]. Prior to this, similar findings were also reported by a group from Leuven as part of an observational study of 21 patients being treated with golimumab in a clinical setting. Median golimumab concentrations were significantly higher in partial clinical responders than in non-responders at week 2 (10.0 vs 7.4 µg/ml, $p = 0.035$) and week 6 (5.1 vs 2.1 µg/ml, $p = 0.037$). Their ROC curve analysis revealed a cut-off of 2.6 µg/ml at week 6 (90% specificity, 56% sensitivity, Area Under the Curve 0.79 [95% CI], $p = 0.034$) for the association with a partial clinical response after 14 weeks of treatment[4]. The authors of both of these studies highlighted the need for further prospective trials to validate their findings and add further validation to commercially available assays for the measurement of golimumab serum concentrations. Data such as these could be used to optimise the use of golimumab in clinical practice and inform prospective therapeutic drug monitoring trials employing trough levels to drive dosing.

Anti-drug antibodies were also detected in a small minority of patients (2.9%) in the PURSUIT trials and the majority of these (67.7%) were found to be neutralizing. Their occurrence was significantly less common in patients who were receiving concomitant

immunomodulators (1.1%) compared with patients who were not (3.8%). However, due to the low observed incidence it is difficult to draw conclusions regarding their impact on efficacy. Nonetheless, a clearer understanding of their impact on drug exposure and subsequently, disease activity would be of benefit in defining the optimal use and monitoring of golimumab.

In conclusion, golimumab is a promising new treatment of moderate-to-severe UC. However, several aspects regarding its optimal use remain unclear. Most important of these is the quantification of a minimum exposure threshold that results in a clinical benefit. This requires dedicated clinical trials to generate the necessary evidence to guide clinicians and allow patients to get the most benefit from this new agent.

References:

1. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous Golimumab Induces Clinical Response and Remission in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology. 2014 Jan;146(1):85-95. PubMed PMID: 23735746.
2. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous Golimumab Maintains Clinical Response in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology. 2014 Jan;146(1):96-109 e1. PubMed PMID: 23770005.
3. Adedokun OJ, Xu Z, Marano CW, Strauss R, Zhang H, Johanns J, et al. Pharmacokinetics and Exposure-response Relationship of Golimumab in Patients with Moderately-to-Severely Active Ulcerative Colitis: Results from Phase 2/3 PURSUIT Induction and Maintenance Studies. Journal of Crohn's & colitis. 2017 Jan;11(1):35-46. PubMed PMID: 27440869. Pubmed Central PMCID: 5175493.
4. Detrez I, Dreesen E, Van Stappen T, de Vries A, Brouwers E, Van Assche G, et al. Variability in Golimumab Exposure: A 'Real-Life' Observational Study in Active Ulcerative Colitis. Journal of Crohn's & colitis. 2016 May;10(5):575-81. PubMed PMID: 26738756. Pubmed Central PMCID: 4957447.

4 Trial Objectives and Design

4.1. Trial Objectives

Primary Objective

To define a week 6 golimumab trough level concentration that predicts response at week 14.

Secondary Objectives

To define golimumab trough level concentrations at weeks 6, 10 and 14 that predict response at each time point, respectively.

To define a golimumab trough threshold that is associated with remission during maintenance therapy.

Tertiary Objectives

Tertiary objectives will centre on the study of the relationship between serum golimumab trough levels and novel disease activity indices (PRO2), biochemical markers of disease activity (CRP, faecal calprotectin) and quality of life indices. The role played by anti-drug antibodies will also be investigated in relation to trough levels and disease activity.

The role played by anti-drug antibodies will be investigated in relation to golimumab trough levels and disease activity.

This study will also generate data that can be used to validate a commercially available golimumab assay as well as a novel patient reported outcome (PRO) assessment of disease activity.

4.1.1 Primary endpoints

Drug exposure to golimumab will be evaluated using serum trough level concentrations measured using a commercially available ELISA produced by Theradiag (LISA TRACKER) at weeks 6 and 10. Clinical UC disease activity will be evaluated using SCCAI with the following definitions:

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

4.1.2 Secondary endpoints

UC disease activity assessments at each time point (weeks 6, 10 and 14) using PRO2, development of anti-drug antibodies, acute infusion reactions (allergic), fecal calprotectin, serum CRP measurements, albumin and QoL assessments using IBD-Control.

4.2 Trial Design

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

The study will involve two study groups:

Cohort 1 (42 patients): Patients commencing golimumab induction therapy will be included in a prospective, observational study.

Cohort 2 (70 patients): Patients receiving golimumab maintenance therapy will be included in a cross-sectional, observational study.

The study will be initiated and primarily run at Guy's and St Thomas' Hospital, a tertiary IBD referral center. To acquire sufficient patient numbers in a timely manner, patients will also be recruited from Kings College Hospital using pre-existing collaborative research links.

The planned inclusion period is estimated to be one and a half years; by which time the target of 112 patients (between the two study cohorts) will be enrolled.

4.3 Trial Flowchart

Patients in Cohort 1 (commencing induction treatment):

	Screen Visit (day -90 – day 0)	Day 0	Day 14	Day 38-42	Day 42	Day 66-70	Day 70	Day 94-98	Day 98
		Week 0	Week 2		Week 6		Week 10		Week 14
Signed Informed consent	X								
Collection of demographic and UC disease related data	X								
Review inclusion/exclusion criteria	X								
Golimumab administration (self-administered by patients)		X	X		X		X		X
Serum golimumab concentration and anti-drug antibody measurements				X		X		X	
Clinical disease activity scores (SCCAI and PRO2)	X			X		X		X	
Injection-site reaction and IBD-relevant concomitant medication review	X[1]			X		X		X	
Serum CRP and albumin measurements	X			X		X		X	
Faecal calprotectin (FC)	X			X		X		X	
Quality of life assessment (IBD-Control)	X			X		X		X	

[1.] Injection site reaction review is not applicable at this visit

Patients in Cohort 2 (on maintenance golimumab treatment):

	Day 0	Screen Visit	Day 21-28	Day 28
Signed Informed consent		X		
Collection of demographic and UC disease related data		X		
Review inclusion/exclusion criteria		X		
Golimumab administration (self-administered by patients)	X			X
Serum golimumab concentration and anti-drug antibody measurements			X	
Clinical disease activity scores (SCCAI and PRO2)			X	
Injection-site reaction and IBD-relevant concomitant medication review		X		
Serum CRP and albumin measurements			X	
Faecal calprotectin (FC)			X	
Quality of life assessment (IBD-Control)			X	

5 Trial Medication

5.1 Investigational Medicinal Product

Golimumab (Simponi®, Janssen Biotech, Inc., Horsham, PA, USA) is a sub-cutaneously administered anti-TNF agent. A homecare agreement is already in place with the golimumab supplier (MSD) and the medicine will be delivered to the patients' home in the standard manner for each site.

5.2 Dosing Regimen

Patients will receive standard golimumab induction treatment of 200 mg at week 0 and 100 mg at week 2, according to standard clinical practice. From week 6 maintenance treatment is started at 100 mg (≥ 80 kg) or 50 mg (< 80 kg) every four weeks. Treatment will be continued until the supervising clinician makes the decision to withdraw treatment (exactly as the standard of care). Enrolment into the trial will have no bearing on this decision.

5.3 IMP Risks

In the controlled period of the pivotal trials in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and UC, upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in 12.6% of golimumab-treated patients compared with 11.0% of control patients. The most serious ADRs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome) and haematologic reactions.

5.4 Drug Accountability

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

5.5 Storage of IMP

A homecare plan (to teach patients how to self-administer injections) is already in place with the golimumab supplier (MSD) and the medicine will be delivered to the patients' home in the standard manner. Standard storage information will be given to patients.

5.6 IMP labelling

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.

5.7 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.

5.8 Concomitant Medication

No restrictions on concomitant medications will be made.
Data regarding IBD-relevant concomitant medications ***only*** will be collected at each visit and recorded on the eCRF.

6 Selection and Withdrawal of Subjects

6.1 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 for cohort 1:

- Aged 18 years or over
- Written informed consent to participate
- Moderate-to-severe UC, defined as:
    - SCCAI > 5 *and,*
        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,

    Evaluated within 4 weeks of screening
- Commencing golimumab treatment
- Sufficient English language skills to understand the patient information sheet and consent form

Inclusion criteria for cohort 2:

- Aged 18 years or over
- Written informed consent to participate
- Receiving golimumab treatment for UC over 14 weeks (have completed 6 injections at time of screening)
- Sufficient English language skills to understand the patient information sheet and consent form

6.2 Exclusion Criteria (cohort 1 only)

- Contra-indication to golimumab: tuberculosis, severe infections or congestive cardiac failure
- Imminent need for colectomy (i.e. colectomy is being planned)
- Previous primary non-response to anti-TNF therapy in the opinion of the investigator
- Previous treatment with more than one anti-TNF therapy (excluding golimumab)

There are no relevant exclusion criteria for patients entering cohort 2.

6.3 Selection of Participants

At Guy's & St Thomas' Hospital 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").

Patients in cohort 1: The decision to commence golimumab treatment will be made in the patients' best interest along standardised clinical treatment algorithms that are in accordance with NICE guidance. Once this decision has been made potential inclusion in GO-LEVEL will be considered. Patients meeting the inclusion criteria will be invited to take part in the study.

Patients in cohort 2: Patients already receiving golimumab treatment will be identified using pharmacy records and patients will be invited to take part in the study.

At King's College Hospital, a similar participant identification plan will be followed with the local Principle Investigator and/or multidisciplinary IBD team identifying potential participants. With the additional step taken that a member of the local clinical care team will contact the potential participant to ask whether they would agree to receive a call from a researcher regarding a study, to which they would be eligible.

To increase recruitment, participants may also be selected using patient identification centres (PIC). Arrangements have been made with Consultant (Dr Leon Pee) and Registrar (Dr Emma Johnston) colleagues at a local secondary care Gastroenterology department: Lewisham University Hospital, Lewisham & Greenwich NHS Trust. A total of approximately 15 minutes per subject is expected to be sufficient for screening records and providing information to potential participants. These additional activities will not be funded but have been agreed with local clinicians, who will also be invited to participate with the publication of the final study results. They may provide a patient information sheet to patients and ask them that if they are interested to contact relevant persons at Guy's & St Thomas'. Alternatively, they may verbally consent patients for their contact details to be forwarded to Guy's & St Thomas'. Once this verbal consent is obtained they will email details using secure @NHS.net to @NHS.net email or by telephone.

6.4 Randomisation procedure/Code-break

This is not a randomised study. Patients who are commencing golimumab treatment will be enrolled into cohort 1. Patients who are already on golimumab maintenance therapy will be enrolled into cohort 2. This will be confirmed as an investigator as part of an eligibility review. Every patient will be appointed a sequential two-digit study number.

6.5 Withdrawal of Subjects

Participants in both study cohorts have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAE's, SUSAR's, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

Should a patient withdraw from study drug ***only***, efforts will be made to continue to obtain follow-up data (including relevant safety assessments), with the permission of the patient. Because this is a non-interventional trial there won't be an interim analysis or premature termination of the study.

Participants who wish to withdraw from trial medication (IMP) will be asked to confirm whether they are still willing to provide the following:

- Trial specific data (clinical and biochemical disease activity scores and quality of life evaluations)
- Data collected as per routine clinical practice

Patient status with regards continuation on the trial will be assessed at every visit and in cases of withdrawal an eCRF withdrawal form will be completed.

6.6 Expected Duration of Trial

The end of the trial will be defined as the date of the final database lock. Each individual subject will remain on the trial until they have completed standard induction therapy with golimumab. The visit at week 14 will be the 'end of study visit' and there will be no additional follow-up visits beyond week 14.

7 Trial Procedures

7.1 By Visit

Cohort 1

Screening visit

- Signed Informed consent
- Review inclusion/exclusion criteria
- Demographic details: age, gender
- IBD-relevant concomitant medication review (Injection site reaction review is not applicable at this visit)
- Baseline clinical (SCCAI and PRO2) and biochemical assessments (CRP, albumin and FC)
- Baseline quality of life assessment (IBD-Control)
- UC disease related details: anatomic distribution (proctitis, left-sided disease or extensive colitis) and duration of disease

Day 0 (week 0), day 14 (week 2), day 42 (week 6), day 70 (weeks 10) and day 98 (week 14)

Patients self-administer golimumab at home.

Any late golimumab administrations (within a week of the planned injection date) would not be considered to significantly impact the integrity of the trial or its results and these will not be considered protocol deviations.

Day 38-42 (week 6), day 66-70 (week 10), day 94-98 (week 14)

- Serum golimumab concentration measurement
- Anti-golimumab antibody measurement
- Injection-site reactions and IBD-relevant concomitant medication review
- Clinical (SCCAI and PRO2) and biochemical assessments (CRP, albumin and FC)
- Quality of life assessment (IBD-Control)

In cohort 1 patients commencing induction therapy with golimumab, will receive delivery of the drug and self-injection training from registered nurses under the Homecare agreement already in place. This will be identical to the standard of care provided by the NHS (both at Guy's & St Thomas' and King's College Hospitals). Routine clinical care would usually involve clinical review prior to treatment initiation and again at approximately 10-14 weeks from treatment initiation. GO-LEVEL will include clinical and biochemical assessments made at weeks 6, 10 and 14, and one of these will be arranged to coincide with their routine clinical appointment. Taking part in the study will therefore involve an additional two visits for patients, above routine clinical care. Patients will be asked to self-administer their treatment in the usual way and visits will be arranged such that trough concentrations will be measured within four days ***prior*** to the subsequent dose. Golimumab injections could be given on the same day as the trial visit but assessments and blood tests must be taken ***prior*** to self-administration.

Cohort 2

Screening visit

- Signed Informed consent
- Review inclusion/exclusion criteria
- Demographic details: age, gender
- Injection-site reaction and IBD-relevant concomitant medication review
- UC disease related details: anatomic distribution (proctitis, left-sided disease or extensive colitis) and duration of disease

Day 0 (week 0)

- Patients self-administer golimumab at home

Day 21-28 (week 4)

- Serum golimumab concentration measurement
- Anti-golimumab antibody measurement
- Clinical (SCCAI and PRO2) and biochemical assessments (CRP, albumin and FC)
- Quality of life assessment (IBD-Control)

Day 28

- Patients self-administer golimumab at home

Any late golimumab administrations (within a week of the planned injection date) would not be considered to significantly impact the integrity of the trial or its results and these will not be considered protocol deviations.

In cohort 2 patients receiving maintenance therapy with golimumab, trough levels will be measured at the next available opportunity after enrollment or at the time of loss of response. In cohort 2, a trough level measurement will be defined as a drug level taken in the final week before the patients next planned injection. Patients may be recruited to cohort 2 in the week leading up to their week 18 injection (i.e. from week 17 after initiation of golimumab onwards).

7.2 Laboratory Tests

For both cohorts, at each time point serum golimumab measurements will be made as well as measurements of antibodies to golimumab, serum CRP and albumin. Routine biochemical measurements (CRP and albumin) will be processed in the standard NHS manner. Agreement is in place with our local reference chemistry laboratory (Viapath) for ELISA measurements of golimumab concentrations and anti-drug antibodies using a commercially available assay (LISA TRACKER, produced by Theradiag). Samples from King's College Hospital for golimumab serum concentrations and anti-drug antibody measurement will be transferred to Vipath via an established sample transfer route.

Fecal calprotectin measurements will also be taken at each study time point (i.e. weeks 6, 10 and 14 in cohort 1 and at a single point in cohort 2). The faecal calprotectin samples will be handled in the standard NHS manner, which involves transfer to the reference chemistry laboratory (via an established sample transfer route) at King's College Hospital.

8 Assessment of Efficacy

Clinical disease activity will be evaluated at each time point (weeks 6, 10 and 14) using the Simple Clinical Colitis Activity Index (SCCAI) and a recently defined two-item (stool frequency and rectal bleeding) patient reported outcome (PRO2) score. Quality of life will be assessed using the IBD-Control questionnaire.

8.1.1 Primary Efficacy Parameters

- Drug exposure to golimumab using serum trough level concentrations.
- Clinical 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)

8.1.2 Secondary Efficacy Parameters

UC disease activity assessments using PRO2, development of anti-drug antibodies, acute infusion reactions (allergic), fecal calprotectin, serum CRP measurements, albumin, QoL assessments using IBD-Control at each time point.

8.2 Procedures for Assessing Efficacy Parameters

For serum trough golimumab levels, anti-drug antibodies and CRP venepuncture will be carried out with 15 ml to be drawn within three days of the subsequent golimumab dose during induction therapy (cohort 1) or one week of subsequent dose during maintenance therapy (cohort 2). Clinical and biochemical disease (calprotectin) activity assessments and quality of life measurements will be collect at weeks 6, 10 and 14 in cohort 1 and week 4 in cohort 2.

9 Assessment of Safety

9.1 Specification, Timing and Recording of Safety Parameters

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

9.2 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 Principle Investigator (and certainly no later than 24hrs) to the KHP-CTO in accordance with the current Pharmacovigilance Policy. All SAEs, SARs and SUSARs are to be reported to MSD's Drug Surveillance Department ("MSD DSD") group by the Chief Investigator, including but not limited to all initial and follow up information involving any study subject.

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.

9.2.1 Adverse events that do not require reporting

AE's will not be collected during the study period but will be managed as per the standard of care. Only injection-site reactions will be collected as AR's during the trial period. They will be managed as per the standard of care.

9.3 Treatment Stopping Rules

Because this is a non-interventional trial there won't be an interim analysis or premature termination of the study. The trial may be prematurely discontinued by the sponsor, chief investigator or regulatory authority on the basis of new safety information or for other reasons given by the regulatory authority or ethics committee.

10 Statistics

To determine a representative cut-off value for golimumab trough levels between the groups of patients stratified by disease activity/response a receiver-operator characteristics (ROC) curve will be created. A trade-off between sensitivity and specificity will be made to establish an adequate lower margin of the therapeutic golimumab range. This statistical plan was reviewed by an independent statistician at King's College London. Relationships between golimumab trough levels and patient characteristics and clinical parameters (albumin, serum CRP, formation of ADA's, fecal calprotectin and IBD-Control) will be evaluated.

10.1 Sample Size

To achieve a power of 80%, with two-sided significance, and to detect a mean difference

in serum concentration of 2 mg/L difference a minimum sample size of 42 patients in each cohort would be required. Increasing the sample size beyond this point would achieve greater power to detect smaller differences in serum concentrations between subgroups.

10.2 Analysis

Descriptive statistics will be used to analyze baseline characteristics. The primary variable of interest will be golimumab drug levels. Other variables will include: efficacy, gender, age, smoking status, concomitant medication, disease location, disease duration, development of anti-drug antibodies, acute infusion reactions, serum CRP, albumin, fecal calprotectin, SCCAI, PRO2, IBD-Control.

Differences between responders and non-responders will be evaluated using a t-test with the threshold for statistical significance set at 0.05. Univariate and bi-variate analysis will be used to assess factors predicting response, including serum golimumab levels at each time point.

11 Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood test reports, X-ray reports, histology reports etc.).

12 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to the Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

Subsequent protocol amendments will be submitted to the REC and Regulatory Authorities for approval, and that the Chief Investigator will comply with regulations, particularly specifying, Pharmacovigilance reporting and providing the REC & MHRA with progress reports, and a copy of the Final Study Report.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

13 Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

14 Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Patient data will be anonymised

- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

14.1 Source Data

Source data regarding eligibility review, demographic details, UC disease-related details, injection-site reactions and concomitant medication as well as clinical disease activity (SCCAI and PRO2) will be documented in the patients electronic notes. Data regarding biochemical disease activity will be printed from EPR and stored in a study specific folder along with quality of life questionnaires. Golimumab serum concentrations and anti-drug antibody measurements will also be stored in the study specific folder.

15 Data Management

Anonymised patient data will be recorded on a bespoke password protected electronic CRF created by King's Clinical Trials Unit. All patient specific data will be recorded using only this number. The full name and birth date will only be recorded on the informed consent form. The study coordinator will monitor patient inclusion and protocol steps, coordinate data entry, perform data analyses and reporting.

16 Publication Policy

Patients are entitled to public disclosure of the results of the trial on the basis of their participation in it. The results of research will be submitted for publication to peer-reviewed scientific journals. Data generated during this study would be of interest and appropriate for publication in the IBD section of high impact general gastroenterology journal (e.g. Gastroenterology, Gut or Clinical Gastroenterology & Hepatology), a specialist IBD journal (Inflammatory Bowel Diseases, The Journal of Crohn's and Colitis) or a specialist Gastroenterology therapeutics journal (Alimentary Pharmacology & Therapeutics). Data in abstract form would be submitted to meetings such as ECCO, BSG, DDW and UEGW.

17 Insurance / Indemnity

No trial-specific insurance/indemnity is in place. Standard NHS insurance/indemnity will apply.

18 Financial Aspects

Funding to conduct the trial is provided in the form of an initial £81,683 grant from Merck Sharp & Dohme (MSD) with a further £15,547 following the increase in recruitment target.

19 Signatures

19.1 CI Signature

_____ _____

Chief Investigator Date

Peter M Irving

19.2 PI Signature

_____ _____

Principle Investigator Date