CLINICAL STUDY REPORT

GO-LEVEL

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

CRN/CPMS:	34486
EudraCT Number:	2017-001374-42
ClinicalTrials.gov Identifier:	NCT03124121
REC Number:	17/LO/1066
IRAS Number:	194917
Investigational Drugs (IMPs):	Golimumab
Indication:	Ulcerative colitis (UC)
Development Phase:	IV
Study Begin (FPFV):	September 2017
Study End (LPLV):	September 2019
Report Version & Issue Date:	Version 1.0, August 25th 2021
Co-sponsor Name and Address:	Amy Holton Guy's & St Thomas' NHS Trust Address: F16 Tower Wing, Guy's Hospital, Great Maze Pond, SE1 9RT
Co-sponsor contact details:	Telephone: 02071885732 Fax: 02071888330 Email: amy.holton@kcl.ac.uk
Chief Investigator:	Peter Irving Guy's and St Thomas' Hospital, Department of Gastroenterology, First Floor College House, North Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH Telephone: 02071882499 Email: peter.irving@gstt.nhs.uk

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.

Chief Investigator:

Printed name	**Signature**	**Date**
Peter Irving		27/AUG/2021

CONTENTS

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 Research Ethics Committee, NHS Health Research Authority).

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
All subjects provided written, informed consent to participate in the study.

2. Data Monitoring

There was no Data Monitoring Committee or Trial Steering Committee

3. Sponsors and Investigators

Co-Sponsors	
Name: Amy Holton ***Guy's & St Thomas' NHS Trust*** ***Address: F16 Tower Wing, Guy's Hospital, Great Maze Pond, SE1 9RT*** ***Telephone: 02071885732*** ***Fax: 02071888330*** ***Email: amy.holton@kcl.ac.uk***	
Chief Investigator ***Name: Peter Irving*** ***Address: Guy's and St Thomas' Hospital, Department of Gastroenterology, First Floor College House, North Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH*** ***Telephone: 02071882499*** ***Email: peter.irving@gstt.nhs.uk***	

4. Co-Investigator(s), Statistician, Laboratories, Database Management

Name: Mark Samaan, Sub-investigator ***Address: Guy's and St Thomas' Hospital, Department of Gastroenterology, First Floor College House, North Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH*** ***Telephone: 07740637713*** ***Email: mark.samaan@gstt.nhs.uk***	***Name: Zehra Arkir, Co-investigator*** ***Address: Viapath Laboratories, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH*** ***Telephone: 020 7188 7188*** ***Email: zehra.arkir@viapath.co.uk***

5. Study Synopsis

Title of clinical trial	Study of the Golimumab Exposure-Response Relationship using Serum Trough Levels
Protocol Short Title/Acronym	GO-LEVEL
Study Phase	IV
Sponsor name	Name: Amy Holton Guy's & St Thomas' NHS Trust Address: F16 Tower Wing, Guy's Hospital, Great Maze Pond, SE1 9RT Telephone: 02071885732 Fax: 02071888330 Email: amy.holton@kcl.ac.uk
Chief Investigator	Chief Investigator Name: Peter Irving Address: Guy's and St Thomas' Hospital, Department of Gastroenterology, First Floor College House, North Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH Telephone: 02071882499 Email: peter.irving@gstt.nhs.uk
Eudract number	2017-001374-42
REC number	17/LO/1066
IRAS project ID:	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 were enrolled into a prospective study (cohort 1). Patients on golimumab maintenance therapy were enrolled into a cross-sectional study (cohort 2).
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.
Planned number of subjects	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: ○ 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 received 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 unless the supervising clinician made the decision to withdraw treatment (as per standard of care).
Active comparator product(s)	N/A
Maximum duration of treatment of a subject	Total duration of treatment was decided by the supervising physician on clinical grounds (as per standard of care) and enrolment into the study had no bearing on this decision.

6. 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

7. Study period (years)

First patient visit (FPFV) 5th September 2017, last patient last visit (LPLV) 19th September 2019. End of trial was defined as database lock, which occurred on 15th February 2021.

8. Phase of development

Phase IV.

9. 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 centred 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 was also investigated in relation to trough levels and disease activity.

GO-LEVEL also generated data used to validate a commercially available golimumab assay as well as a novel patient reported outcome (PRO2) assessment of disease activity.

10. Background and Context

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.

11. Methodology

GO-LEVEL was an open-label, non-randomised, phase IV trial of golimumab for UC. The study involved two study groups:

- Cohort 1 (42 patients): Patients commencing golimumab induction therapy for active UC were included in a prospective, observational study.
- Cohort 2 (70 patients): Patients receiving golimumab maintenance therapy for UC were included in a cross-sectional, observational study.

Patients received 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 unless the supervising clinician made the decision to withdraw treatment (as per standard of care).

Potential participants were identified by members 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 were discussed at a multidisciplinary meeting ("Virtual Biologics and Immunosuppressant Clinic, VBIC"), where appropriateness for enrollment was assessed.

Trial Procedures 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-administered golimumab at home.

Any late golimumab administrations (within a week of the planned injection date) were not considered to significantly impact the integrity of the trial or its results and therefore, were not 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, received delivery of the drug and self-injection training from registered nurses under an agreement with Healthcare at Home. This was identical to the standard of care provided by the NHS. Patients were asked to self-administer their treatment in the usual way and study visits were arranged such that trough concentrations were measured within four days ***prior*** to the subsequent dose. Golimumab injections could have been given on the same day as the trial visit but assessments and blood tests were 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-administered 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-administered golimumab at home

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

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

Schedule of events

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	

Trial Medication
Golimumab (Simponi®, Janssen Biotech, Inc., Horsham, PA, USA) is a sub-cutaneously administered anti-TNF agent.

Dosing Regimen
Patients received 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 was started at 100 mg (patients with body weight≥ 80 kg) or 50 mg (patients with body weight< 80 kg) every four weeks.

12.Number of patients

Induction cohort
Patient characteristics and flow
A total of 42 patients commencing golimumab induction therapy were recruited; 38 completed the 14-week study protocol (table 1). Two patients discontinued due to disease progression and commencement of an alternative therapy and one discontinued treatment due to a serious adverse event (facet joint infection, details included in safety section of supplementary online material). They were therefore excluded from the pharmacokinetic analyses but were included in treatment outcomes as non-responders. One patient was excluded from analysis due to protocol violation and was excluded.

Maintenance cohort
Patient characteristics and flow
A total of 70 patients receiving golimumab maintenance therapy (defined here as >18 weeks from first dose) were recruited; 66 of these were included in the final analyses (table 5). Three patients were excluded from analysis for protocol violations and one patient due to their therapeutic drug monitoring sample being unsuitable for analysis.

13. Diagnosis and main criteria for inclusion

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

Exclusion Criteria (cohort 1 only)

- Contra-indication to golimumab: tuberculosis, severe infection 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 were no relevant exclusion criteria for patients entering cohort 2.

14. Test product, dose and mode of administration

Baseline therapy
As patients were treated as per standards of care, no stipulations were made regarding co-therapy. Specifically, patients could be treated with mesalazine, immunomodulators and steroids during the study protocol. Topical (per rectal therapies were also allowed.

Investigational medical product
Golimumab

Dose of IMP administered to each study participant

All patients in the induction cohort received 200 mg golimumab at week 0 and 100mg at week 2. Of the 38 patients in the induction cohort, 20 received 100 mg dosing from week 6 onwards and 18 received 50 mg dosing.

Of the 66 patients in the maintenance cohort 30 were receiving 50 mg golimumab every 4 weeks, and 36 were on 100 mg golimumab every 4 weeks.

15. Duration of treatment

The induction study cohort protocol lasted 14 weeks. The visit at week 14 was the 'end of study visit' and there were no additional follow-up visits beyond this. However, patients could discontinue golimumab treatment during this period if considered in their best interests by their supervising clinician (as per standard of care).

16. Reference therapy, dose and mode of administration

Not applicable

17. Criteria for evaluation: Endpoints

Primary: golimumab trough levels and UC disease activity (SCCAI) at weeks 6 and 10

- 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)

Secondary: 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.

18. Criteria for evaluation: Safety

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, congestive cardiac failure, autoimmune processes (lupus-like syndrome) and haematologic reactions. In the controlled period of large-scale golimumab trials, serious infections were observed in 1.2% of golimumab-treated patients.

All SAEs, SARs and SUSARs were reported within 24 hours by the Principal Investigator to the KHP-CTO in accordance with the current Pharmacovigilance Policy. All SAEs, SARs and SUSARs were 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 were responsible for reporting SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial took place. The Chief Investigator reported to the relevant ethics committee. The Chief Investigator and KHP-CTO submited a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

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

Overall, golimumab was well tolerated but 5 SAEs and 1 SAR were observed (please see *Safety - Summary of treatment-emergent SAEs and SARs* section for details). One of these was for a serious infection, a rate which is in keeping with data from large-scale randomised trials. No new safety signals were observed as part of the GO-LEVEL study.

19.Statistical Methods

Study evaluations

Induction cohort evaluations were carried out at baseline and after 6, 10 and 14 weeks of treatment. Visits were arranged within 4 days prior to subsequent golimumab administrations for the purpose of serum golimumab concentration measurements being at, or at least close to, trough. Each study visit included assessments of clinical disease activity, quality of life and biochemical activity. Maintenance cohort evaluations included the same assessments and were carried out within 7 days prior to subsequent golimumab administrations.

Clinical disease activity

Clinical disease activity was primarily evaluated using SCCAI with clinical remission defined as an SCCAI≤2 and response as an SCCAI≤5, with a decrease by ≥2. PRO2 was recorded alongside SCCAI.

Quality of life

Quality of life was evaluated using the IBD-Control-8 index, which includes a 100mm visual analogue scale (VAS). IBD-Control-8 ranges from 0 to 16 with higher scores indicating better quality of life. Higher scores on the VAS (ranging 0-100) also indicate better quality of life.

Biochemical disease activity

Biochemical disease activity was evaluated using serum CRP and faecal calprotectin (FC) measurements. FC was measured using the fCal assay (Bühlmann, Switzerland).

Measurement of serum golimumab and anti-golimumab antibody concentrations

Samples were processed according to the instructions provided by the manufacturers, using a commercially available ELISA (LISA TRACKER, Theradiag, France). This assay is drug-sensitive and therefore, is only able to detect antidrug antibodies in when drug levels are low or absent. AGA were considered present at titres ≥10ng/ml.

Statistical analysis

Continuous data were summarised as medians and range (in brackets). Paired SCCAI, CRP and FC values were compared using Wilcoxon signed-rank test. 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). Receiver operating characteristics (ROC) curve analysis was used to identify target thresholds. Chi-squared test for trend (also known as the Cochrane-Armitage test for trend) was used to analyse quartile data. Univariate and multivariate linear regression analyses were performed to explore factors predictive of golimumab serum concentrations. Univariate and multivariate logistic regression analyses were used to evaluate factors predictive of treatment response. Analyses were carried out using GraphPad Prism v8.2.1 and IBM SPSS v25.

20.Summary

Induction cohort demographics and baseline characteristics

Characteristics of patients included in pharmacokinetic analyses	**n = 38**
Gender, male:female, n (%)	22:16 (58:42)
Median age (range), years	37 (24-48)
Median disease duration (range), years	7 (0.5-28)
Median body mass index (range)	24.3 (17.9-39.0)
Median faecal calprotectin (range), µg/g, n=39	426 (5-5420)
Disease extent, n (%)	
Proctitis	2 (5)
Left-sided	20 (53)
Extensive	16 (42)
Concomitant immunomodulation, n (%)	
None	15 (39)
Thiopurine	20 (53)
Methotrexate	3 (8)
Corticosteroids, n (%)	16 (42)
Prior anti-TNF experience, n (%)	
Naïve	36 (95)
Exposed	2 (5)

Maintenance cohort demographics and baseline characteristics

Characteristic	**n = 66**
Gender, male:female, n (%)	37:29 (56:44)
Median age (range), years	35.5 (20-73)
Median body mass index (range)	23.7 (18.2-39.0)
Median disease duration (range), years	8 (0.6-28.8)
Median duration on golimumab (range), months	6 (5-34)
Disease extent, n (%)	
Proctitis	5 (8)
Left-sided	35 (53)
Extensive	26 (39)
Concomitant immunomodulation, n (%)	
None	20 (30)
Thiopurine	43 (66)
Methotrexate	3 (4)
Corticosteroids, n (%)	6 (9)
Prior anti-TNF experience, n (%)	
Naïve	61 (92)
Exposed	5 (8)

Primary outcome

Outcome (n = 38)		Baseline	Week 6	p-value vs baseline	Week 10	p-value vs baseline	Week 14	*p*-value vs baseline
Clinical disease activity, median (range)	SCCAI	8 (5-15)	2 (0-12)	<0.0001	1.5 (0-12)	<0.0001	2 (0-13)	<0.0001
	PRO2	4 (2-6)	0.5 (0-5)	<0.0001	0 (0-5)	<0.0001	1 (0-5)	<0.0001
Quality of life, median (range)	IBD-Control-8	3 (0-14)	11 (2-16)	<0.0001	12 (0-16)	<0.0001	12.5 (0-16)	<0.0001
	IBD-Control-VAS	35 (2-80)	64.5 (18-100)	<0.0001	69.5 (17-100)	<0.0001	75 (20-100)	<0.0001
Biochemical disease activity, median (range)	CRP, mg/L	2 (1-50)	1 (1-34)	0.071	1 (1-33)	0.0078	1 (1-50)	0.0010
	FC, µg/g	426 (5-5420)	109 (5-2920)	0.021	126 (5-2800)	0.0022	46 (5-2000)	0.0003
	Albumin, g/L	45 (35-51)	46 (33-56)	0.0027	45.5 (33-52)	0.0046	46 (33-52)	0.0013

Clinical, biochemical and quality of life outcomes for induction cohort patients at baseline and weeks 6, 10 and 14

Median serum golimumab concentrations amongst patients who achieved a clinical response, clinical remission and combined clinical-biochemical remission compared to those who did not at weeks 6, 10 and 14

		Median serum golimumab concentration, µg/ml		
		Week 6	**Week 10**	**Week 14**
Clinical response	Achieved	4.7	2.8	2.1
	Not achieved	3.0	2.6	1.9
	p-value	0.09	0.38	0.27
Clinical remission	Achieved	4.8	2.5	2.2
	Not achieved	3.0	2.7	1.8
	p-value	0.02	0.77	0.13
Combined clinical-biochemical remission	Achieved	5.0	2.5	2.4
	Not achieved	3.0	3.4	1.8
	p-value	0.02	0.42	0.08

21. Safety - Summary of treatment-emergent SAEs and SARs

Five serious adverse events (SAE) were observed as part of the GO-LEVEL induction cohort, two of which involved a single patient and one of which was classified as a serious adverse reaction (SAR).

SAE 1/SAR: Patient with active disease despite being established on azathioprine and recent introduction of prednisolone. Shortly after second dose of golimumab developed lower back pain and fever and was admitted under orthopaedics. An MRI scan showed inflammation in right L4/L5 facet joint with surrounding fat stranding considered suggestive of infection. In view of this azathioprine and golimumab were discontinued (his prednisolone reducing regimen had recently completed). Patient was commenced on IV antibiotics.

SAE 2: Failure to respond to golimumab (evidenced by ongoing symptoms and a rise in FC from 467µg/g at baseline to >1800µg/g at week 6) and was admitted for rescue infliximab. This too failed and a colectomy was performed, at approximately 8 weeks after his first dose of golimumab.

SAE 3: Failure to respond to the first two injections of golimumab and was admitted for deteriorating symptoms at approximately week 3. His oral prednisolone was switched to IV hydrocortisone and golimumab switched to infliximab, to which he responded and was discharged.

SAE 4: Patient with steroid refractory, severely active disease at baseline (Mayo endoscopic score 3), who was commenced on azathioprine and golimumab concurrently developed azathioprine induced pancreatitis. Serum amylase at the time of admission was 641U/L and this settled with azathioprine discontinuation and conservative management.

SAE 5: Patient admitted with an ulcerative colitis flare and commenced on golimumab as part of induction cohort. In patient stay was extended for an additional day due to abdominal discomfort following a flexible sigmoidoscopy.

No serious adverse events were reported by patients taking part in the GO-LEVEL maintenance cohort. No injection site reactions (AR's of special interest) were observed.

22. Conclusion

GO-LEVEL demonstrates a relationship between golimumab exposure and favourable treatment outcomes including reductions in both clinical and biochemical disease activity, during both induction and maintenance therapy. Future randomised studies including proactive therapeutic drug monitoring and serum threshold-driven dosing are necessary to investigate whether these findings represent a causal association.

23. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated August 25th 2021.

24. Reference

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.