ISRCTN18820528 https://doi.org/10.1186/ISRCTN18820528

Identifying markers of successful dose reduction in the maintenance phase of tofacitinib treatment of ulcerative colitis

Submission date	Recruitment status	[X] Prospectively registered
09/08/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
07/09/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
20/11/2024	Digestive System	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Tofacitinib is an orally administered drug that has been shown to be effective in patients with moderate to severe ulcerative colitis (UC), an incurable, chronic inflammatory condition of the large bowel. The tofacitinib clinical trials demonstrate that the 10mg twice daily maintenance dose is superior to the 5mg twice daily dose in those with prior treatment failure for UC. Accordingly, many practitioners favour continuing the 10mg twice daily dose in higher-risk patients with prior treatment-resistant disease, rather than dropping to the 5mg twice daily maintenance dose at week 8 (or week 16 in those slower to respond).

This dosing decision needs to be balanced against the potential risk of continuing at the higher dose; there is a higher risk of side effects such as infection and blood clots with the 10mg twice daily dose.

Given that most patients who are receiving tofacitinib are treatment resistant, there is an urgent need to identify ways to predict which patients are more likely to flare should their dose reduce. Such biomarkers would enable us to risk stratify our patients at the point of consideration of dose reduction, to enable assessment of the risk and benefit of dose reduction versus continuation at the higher dose.

This study aims to explore clinical and laboratory-based markers (from blood and colon tissue), which in turn may to help make key treatment decisions for tofacitinib-treated patients. We hypothesise that patients who relapse following dose reduction will have changes in cytokine expression of their pro-inflammatory T cells in peripheral blood mononuclear cells (PBMCs), increased STAT activation in PBMCs, and possibly signature genes in their colonic tissue.

Who can participate?
Adults aged 18 years or above with a history of ulcerative colitis, as defined by standard clinical criteria and who are having their tofacitinib dose reduced from 10mg BD to 5mg BD in view of an adequate response, as decided by their treating clinical team, and are undergoing routine endoscopy.

What does the study involve?
Participants will go ahead with participants flexible sigmoidoscopy (camera test) as planned. The endoscopist will take a series of 12 extra biopsies for this study in addition to 2-4 standard biopsies. The biopsy samples will be used for two purposes; 1, to make another assessment of how active participants' colitis is and 2, to carry out scientific analysis to identify genes that may act as predictors of relapse. This analysis aims to study RNA (a photocopy of the DNA), which acts as a messenger and can give important clues about the processes that occur within the bowel during disease relapse.

Immediately following the procedure, in addition to standard baseline blood tests we will also take an additional vial of blood for this study (approximately 5 teaspoons). This will be to allow us to perform analyses looking for inflammatory messengers and markers that may predict relapse.

Should participants undergo another flexible sigmoidoscopy if participants were to relapse, and after 44 weeks of dose reduction as is standard, the study biopsies and blood tests will be repeated in addition to standard tests. Otherwise, participants will be managed by the participants treating team in the standard way. Participants' participation in the study will end if the relapse means that participants need to stop tofacitinib and commence a different drug, or if the relapse means that participants require surgery to remove the large bowel. Participating in this study will not affect how participants are treated. We will monitor participants' progress and collect participants' data that will come from participants' standard investigations and management.

What are the possible benefits and risks of participating?
Although there are no direct benefits to the patient by taking part, the results and analyses from this study may help other patients who have ulcerative colitis and are being treated with tofacitinib.

Where is the study run from?
Guy's and St Thomas' NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
August 2019 to October 2023

Who is funding the study?
Pfizer (UK)

Who is the main contact?
Dr Sailish Honap, shonap@nhs.net

Contact information

Type(s)
Public

Contact name
Dr Sailish Honap

ORCID ID
https://orcid.org/0000-0001-6657-2763

Contact details
Department of Gastroenterology
St Thomas' Hospital
Westminster Bridge Road
Lambeth
London
United Kingdom
SE1 7EH
+44 (0)207 1882499
shonap@nhs.net

Type(s)
Scientific

Contact name
Dr Peter Irving

ORCID ID
https://orcid.org/0000-0003-0972-8148

Contact details
Department of Gastroenterology
St Thomas' Hospital
Westminster Bridge Road
Lambeth
London
United Kingdom
SE1 7EH
+44 (0)2071882499
peter.irving@gstt.nhs.uk

Type(s)
Scientific

Contact name
Dr Susan John

ORCID ID
https://orcid.org/0000-0002-5620-1982

Contact details
Department of Immunobiology
Floor 2, Borough Wing
Guy’s Hospital
St Thomas’ Street
London
United Kingdom
SE1 9RT
+44 (0)2071889614
susan.john@kcl.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
276727

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 276727, CPMS 49789

Study information

Scientific Title
Biomarkers of Relapse In ulcerative colitis patients after Tofacitinib dose rEduction (BRITE)

Acronym
BRITE

Study objectives
We hypothesise that patients who relapse following maintenance dose reduction of tofacitinib will have increased markers of pro-inflammatory effector T cells in peripheral blood and inflamed mucosal tissue. The principal questions we aim to address are as follows;

1. Is there increased activation of STAT proteins in peripheral blood in patients who relapse?
2. Are there changes in cytokine expression in peripheral T cells that predict relapse?
3. Can we identify signature gene(s) that serve as a biomarker to predict relapse?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/08/2021, Yorkshire & The Humber - Leeds East Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8018; leedseast.rec@hra.nhs.uk), ref: 21/YH/0148

Study design
Prospective multi-centre observational study

Primary study design
Observational

Study type(s)
Treatment

Health condition(s) or problem(s) studied

Adult patients in the maintenance phase of tofacitinib treatment of ulcerative colitis

Interventions
This is a prospective, observational, investigator-initiated study with an overarching objective to identify biochemical and genetic markers of patients more likely to flare after tofacitinib dose reduction. This will eventually allow us to target continued higher dosing of 10mg bd at those patients who are most likely to benefit from it and avoid its use in patients in whom it is potentially unnecessary. Thereby, it would enable using the drug in a safer, more effective, and more economical manner.

We will prospectively enrol a cohort of 50 UC patients who have achieved an adequate response to tofacitinib at a dose of 10mg bd and whose dose is being reduced to 5mg bd. Post-induction flexible sigmoidoscopy will be performed as part of routine clinical care and colonic tissue and blood samples will be collected at study entry. Patients' disease course will be followed-up through routine care to the point of flare, or week 44 post-induction.

Briefly, to address the study questions above, we will firstly monitor the phosphorylation of STAT proteins in peripheral blood mononuclear cells from patients enrolled in the study, with blood drawn before dose reduction and at the point of flare. Secondly, we will evaluate cytokine expression in peripheral CD4 T cells to see if there are any changes that predict relapse. Finally, we will compare gene expression profiles from colonic tissue of patients who remain symptomless on the lower dose of tofacitinib with those patients who ultimately show clear clinical signs of relapse.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tofacitinib

Primary outcome(s)
At week 44 and at relapse (if applicable):
1. Clinical status (simple clinical colitis activity index and partial Mayo score)
2. C-reactive protein and faecal calprotectin
3. Histological markers of disease activity (Nancy histological index)
4. STAT activation in peripheral blood mononuclear cells
5. Cytokine expression in peripheral T cells
6. Gene signatures in colonic biopsies

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
31/10/2023

Eligibility

Key inclusion criteria

1. Aged 18 years or over, either male or female
2. A history of ulcerative colitis, as defined by standard clinical criteria
3. Patients who are having their tofacitinib dose reduced from 10mg BD to 5mg BD in view of adequate response, as decided by their treating clinical team, and are undergoing routine endoscopy.
4. Sufficient English language skills to understand the patient information sheet and consent form.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
50

Key exclusion criteria
1.Patients undergoing dose reduction for reasons other than adequate response to 10mg bd (ie. active infection or VTE risk).
2. Patients being dose reduced without undergoing endoscopy
3. Patients with insufficient English language skills to understand the patient information sheet and consent form.

Date of first enrolment
10/09/2021

Date of final enrolment
01/09/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Thomas' Hospital
IBD Centre

Department of Gastroenterology
1st Floor College House
South Wing
London
United Kingdom
SE1 7EH

Sponsor information

Organisation
Guy's and St Thomas' NHS Foundation Trust

ROR
https://ror.org/00j161312

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Industry

Funder Name
Pfizer

Alternative Name(s)
Pfizer Inc., Pfizer Consumer Healthcare, Davis, Charles Pfizer & Company, Warner-Lambert, King Pharmaceuticals, Wyeth Pharmaceuticals, Seagen, Pfizer Inc

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			20/09/2023	No	No
Participant information sheet	version 2.0	03/08/2021	11/08/2021	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 1.0	07/06/2021	13/08/2021	No	No