

# The impact of pausing BTKi therapy and responsiveness of vaccination in blood cancer patients: A randomised controlled study – the IMPROVE study

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<b>Registration date</b> 20/09/2022	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 03/04/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Chronic lymphocytic leukaemia (CLL) is a blood cancer that affects the white blood cells called lymphocytes. It is the commonest adult leukaemia, with 3,800 people diagnosed each year in the UK. It is more common in people aged over 60 years. Currently some 31,900 people have CLL in the UK.

CLL develops slowly and there is no cure. People with CLL have a weakened immune system and are susceptible to infections. These infections can be severe and life-threatening. New drugs called Bruton Tyrosine Kinase inhibitors (BTKi) have transformed the outlook for CLL patients, however they stop the immune response to vaccination. They need to be taken daily and continuously. They are sometimes paused if a patient needs an operation. In the UK, they are used at all stages of treatment. The IMPROVE study aims to find out:

Does pausing BTKi inhibitor drugs for a total of three weeks before and after having the COVID vaccine improve the antibody response and is this well tolerated?

### Who can participate?

Adults with well-controlled CLL who have been taking a BTKi inhibitor for at least a year, and are due to have a COVID vaccine

### What does the study involve?

The study aims to recruit 120 people at up to 10 NHS hospital sites. Half (60) will be asked to pause their treatment for three weeks: one week before their vaccine, and two weeks after. The other half (60) will continue their treatment as usual. Blood samples will be taken to check everyone's vaccine response three weeks and 12 weeks after vaccination. The participant's CLL will also be monitored and participants will be asked to complete questionnaires about their quality of life.

### What are the possible benefits and risks of participating?

In March 2020 everyone with CLL was advised to shield. To date, most people with CLL continue

to shield as best they can. Advice from haematologists is to be as careful as possible. This means they are largely trapped in their homes, feeling increasingly left behind as the rest of society moves on. It is now COVID-19 that is restricting life for people with CLL and their families, rather than their CLL. The problem is people with CLL have very poor responses to COVID-19 vaccines in comparison to the general population. For those on BTKi inhibitor drugs, it is a double whammy as the drugs make it even more unlikely that patient will respond to COVID-19 vaccination. As COVID-19 is here to stay, further vaccine doses are likely to be recommended for clinically vulnerable patients. The IMPROVE study aims to see if this 3 week's pausing of BTKi therapy would help protect people with CLL and allow them to resume a more normal life.

With regards to risks, to participate in the study, 3 blood samples need to be taken – so there are the risks that come with a blood sample being taken. The questions/questionnaires used in this study are not mandatory and do not ask questions that might embarrass a participant.

Improving vaccination responses has been a hot topic between clinicians and the CLL community for many years. COVID-19 has made this a priority. People with CLL co-designed the IMPROVE study and are partners in governing, managing and advising throughout the study.

Where is the study run from?

The study is overseen by the University of Birmingham, and the Chief Investigator, Dr Helen Parry is based there. Researchers and those experienced in running clinical studies are managing the study at the University of Oxford. The researchers in Oxford are specifically based in the Oxford Clinical Trials Research Unit (OCTRU). Participants are aimed to be recruited from NHS hospitals across the UK that have the permissions to approach participants to consider taking part in the IMPROVE study.

When is the study starting and how long is it expected to run for?

August 2022 to January 2024

Who is funding the study?

National Institute for Health and Social Care Research (NIHR), Efficacy and efficiency mechanism (EME) programme (UK)

Who is the main contact?

improve@ndorms.ox.ac.uk

## Contact information

**Type(s)**

Public

**Contact name**

Dr Vicki Barber

**ORCID ID**

<https://orcid.org/0000-0001-9631-3666>

**Contact details**

OCTRU

Botnar Research Centre

University of Oxford

Windmill Road  
Oxford  
United Kingdom  
OX3 7LF  
+44 (0)1865223469  
improve@ndorms.ox.ac.uk

## **Additional identifiers**

### **Clinical Trials Information System (CTIS)**

Nil known

### **Integrated Research Application System (IRAS)**

319057

### **Protocol serial number**

IRAS 319057, CPMS 53957

## **Study information**

### **Scientific Title**

A multi-centre randomised controlled trial examining the effects of temporarily pausing Bruton Tyrosine Kinase inhibitor therapy to coincide with SARS-CoV-2 vaccination and its impact on immune responses in patients with Chronic Lymphocytic Leukaemia

### **Acronym**

IMPROVE

### **Study objectives**

The aim of this study is to assess whether a temporary three-week pause of daily Bruton tyrosine kinase inhibitor (BTKi) treatment around SARS-CoV-2 vaccination improves the immune response in people with chronic lymphocytic leukaemia (CLL) whilst maintaining disease control.

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

Approved 09/09/2022, Leeds East Research Ethics Committee (Yorkshire and the Humber – Leeds East, NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8105, +44 (0)2071048170; leedseast.rec@hra.nhs.uk), ref: 22YH0226

### **Study design**

Multicentre parallel-group two-arm superiority open-label randomized controlled study

### **Primary study design**

Interventional

### **Study type(s)**

Other

## **Health condition(s) or problem(s) studied**

Chronic lymphocytic leukaemia

## **Interventions**

The intervention is a 3-week temporary pause (suspension) of existing ongoing BTKi therapy. The 3-week temporary pause starts 1 week before vaccination 6 days of no BTKi administration, then on day 7 of no BTKi – COVID vaccination is received and then another 14 days of no BTKi administration – in total 21 days of tablets are omitted). The BTKi therapy being paused will either be Acalabrutinib or Ibrutinib at any dose, and those participating in the study will have been on a BTKi for at least 12 months prior to study enrolment. The control group will not have any pausing in the BTKi administration for the purpose of COVID vaccination.

All participants will have data collection at Baseline (pre-vaccination), 3 weeks post-COVID vaccination and 12 weeks post-COVID vaccination.

Blood sampling will occur at each of these timepoints. Participants will be invited into clinics for blood sampling, and data collection. Participants will also have the option to answer some of the questionnaires at 3 and 12 weeks electronically before attending the clinic visit.

Participants are randomised when they know they have a confirmed COVID vaccination date and are randomised using an online tool by researchers in IMPROVE. Randomisation allocations will be including stratification and participants will equally (1:1) to intervention and control arms based on the stratification factor of the BTKi therapy the participant is taking – their first line or subsequent therapy for CLL.

## **Intervention Type**

Other

## **Primary outcome(s)**

Anti-SARS-CoV-2 spike (S) protein receptor binding domain (RBD) antibody levels measured using Roche Elecsys® electrochemiluminescence assay (Roche S) at baseline and at 3 weeks post-SARS-CoV-2 vaccination

## **Key secondary outcome(s)**

1. Anti-spike (IgG, IgA and IgM) RBD antibody levels measured using Roche Elecsys® electrochemiluminescence assay (Roche S) at baseline and at 12 weeks post-SARS-CoV-2 vaccination
2. Neutralising antibody titre levels at 50% and 90% against Wuhan D614G (B.1) and the current variant of concern (VOC) ) will be assessed using validated laboratory methods at baseline, 3 and 12 weeks post SARS-CoV-2 vaccination
3. Antigen-specific T-cell response for ancestral Wuhan and 1 x VOC spike, and combined nucleocapsid and membrane response measured using the enzyme-linked immunosorbent spot (ELISpot) assay at baseline and 3 weeks post-SARS-CoV-2 vaccination
4. Antibody response to 4 strains of influenza present in the Autumn 22 vaccine (continuous OD 450nm read out) measured using ELISA [For those who receive flu vaccination only] at baseline and 3 weeks post SARS-CoV-2 vaccination
5. Disease activity questions (raised temperature, enlarged or new lymph nodes) measured using a non-validated questionnaire answered by participants electronically at baseline, 3 and 12 weeks post-SARS-CoV-2 vaccination or a participant attending their 3-week clinic visit – if the adherence questions have not been completed they will be asked to complete the questions at that visit
6. Full Blood Count (Haemoglobin, platelet levels and lymphocyte levels) measured using

standard medical laboratory methods at baseline, 3 and 12 weeks post SARS-CoV-2 vaccination

7. Blood Film (presence of new prolymphocytes, smear cells or lymphocytosis) measured using standard medical laboratory methods at baseline, 3 and 12 weeks post SARS-CoV-2 vaccination

8. Lactate dehydrogenase levels measured using standard medical laboratory methods at baseline, 3 and 12 weeks post SARS-CoV-2 vaccination

9. Health-related quality of life (HRQoL) measured using the EORTC-QLQ-CLL17 scales (symptom burden, physical condition/fatigue, and worries/fears on health and functioning) at baseline, 3 and 12 weeks post-SARS-CoV-2 vaccination

10. Self-reported adherence measured using a non-validated questionnaire answered by participants electronically at 3 weeks post-SARS CoV-2 vaccination – or a participant attending their 3-week clinic visit – if the adherence questions have not been completed they will be asked to complete the questions at that visit

**Completion date**

31/01/2024

## Eligibility

**Key inclusion criteria**

1. Aged 18 years and over
2. Confirmed diagnosis of chronic lymphocytic leukaemia
3. Taking oral NICE-approved BTKi therapy (Acalabrutinib or Ibrutinib) for at least 12 months since the date of initiation of therapy
4. Has achieved complete remission (CR; including CR with incomplete marrow recovery), partial remission (PR; including nodular PR or PR with lymphocytosis) or stable disease by the International Workshop on CLL (iwCLL) response criteria
5. Considered able to temporarily pause (suspend) BTKi therapy for three weeks without the risk of a substantial increase in disease activity
6. Anticipated to take BTKi over the next 4 months (i.e. not in the STATIC trial arm where therapy is stopped)
7. Willing to accept either study arm allocation
8. Able to give informed consent
9. Eligible for a planned vaccination for COVID-19

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**Total final enrolment**

**Key exclusion criteria**

1. Insufficient time for applying the intervention prior to the planned COVID-19 vaccination.
2. Diagnosed with alternative conditions requiring treatment with BTKi
3. Treated with anti-CD20 antibody therapy in the last 18 months or planning to start it
4. Concurrent immune suppressive treatments in the last 3 months specifically: methotrexate, ciclosporin, BCL-2 inhibitors, azathioprine, mycophenolate, prednisolone, biologic agents
5. Any contraindication to COVID-19 vaccination
6. Richter's transformation requiring active therapy
7. Radiotherapy or cancer chemotherapy in the last 6 months
8. Active solid organ cancer (people with skin cancer or those cured of solid organ cancer are eligible)
9. Receiving or has received in the past 6 months immunoglobulin replacement therapy
10. Receiving or has received in the past 6 months monoclonal antibody against COVID-19 spike protein

**Date of first enrolment**

23/09/2022

**Date of final enrolment**

30/06/2023

**Locations****Countries of recruitment**

United Kingdom

England

**Study participating centre**

**University Hospitals Birmingham NHS Foundation Trust**

Queen Elizabeth Hospital

Mindelsohn Way

Edgbaston

Birmingham

United Kingdom

B15 2GW

**Study participating centre**

**Kings College Hospital Department of Haematology**

Kings College Hospital

Denmark Hill

London

United Kingdom

SE5 9RS

**Study participating centre**  
**Royal Stoke University Hospital**  
Newcastle Road  
Stoke-on-trent  
United Kingdom  
ST4 6QG

**Study participating centre**  
**Nottingham University Hospitals NHS Trust - City Campus**  
Nottingham City Hospital  
Hucknall Road  
Nottingham  
United Kingdom  
NG5 1PB

**Study participating centre**  
**Oxford University Hospitals NHS Foundation Trust**  
Oxford Cancer and Haematology Centre  
Oxford  
United Kingdom  
OX3 7LE

**Study participating centre**  
**Sandwell Healthcare NHS Trust**  
Sandwell District General Hospital  
Lyndon  
West Bromwich  
United Kingdom  
B71 4HJ

**Study participating centre**  
**The Dudley Group NHS Foundation Trust**  
Russells Hall Hospital  
Pensnett Road  
Dudley  
United Kingdom  
DY1 2HQ

**Study participating centre**

**University Hospitals Coventry and Warwickshire NHS Trust**

Walsgrave General Hospital  
Clifford Bridge Road  
Coventry  
United Kingdom  
CV2 2DX

**Study participating centre**

**Glan Clwd Hospital**

Ysbyty Glan Clwydd  
Bodelwyddan  
Rhyl  
United Kingdom  
LL18 5UJ

**Study participating centre**

**University Hospitals Plymouth NHS Trust**

Derriford Hospital  
Derriford Road  
Crownhill  
Plymouth  
United Kingdom  
PL6 8DH

**Study participating centre**

**Aneurin Bevan University Local Health Board**

St. Cadoc's Hospital  
Lodge Road  
Caerleon  
Newport  
United Kingdom  
NP18 3XQ

## **Sponsor information**

**Organisation**

University of Birmingham

**ROR**

<https://ror.org/03angcq70>

# Funder(s)

## Funder type

Government

## Funder Name

Efficacy and Mechanism Evaluation Programme

## Alternative Name(s)

NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

## Funding Body Type

Government organisation

## Funding Body Subtype

National government

## Location

United Kingdom

# Results and Publications

## Individual participant data (IPD) sharing plan

The sponsor will retain ownership of all data arising from the study.

Participant level dataset and statistical code will be made available upon reasonable request to OCTRU and the CI, once the IMPROVE study findings have been published in full. Some specific data items may not be shared in order to maintain participant anonymity.

## IPD sharing plan summary

Available on request

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>		01/04/2025	03/04/2025	Yes	No
<a href="#">Protocol article</a>		28/09/2023	29/09/2023	Yes	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes