

# A trial evaluating the effectiveness of combining standard R-CHOP treatment with acalabrutinib in patients with newly diagnosed diffuse large B-cell lymphoma

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<b>Registration date</b> 16/08/2021	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 07/07/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-acalabrutinib-for-diffuse-large-b-cell-lymphoma-remodl>

### Background and study aims

Diffuse large B-cell lymphoma (DLBCL) is the most common of the non-Hodgkin's lymphomas. Non-Hodgkin lymphoma is a type of cancer that develops in the lymphatic system, a network of vessels and glands spread throughout your body.

Whilst the majority of patients will respond well to conventional treatment (R-CHOP a type of immunochemotherapy), a significant number of patients with lymphoma will not respond to initial therapy or their disease will return after completion of therapy. In a number of B-cell diseases an enzyme called Bruton tyrosine kinase (BTK) prevents death of tumour cells, including in DLBCL. Acalabrutinib is an orally active BTK inhibitor and it is thought that stopping BTK from being activated may help in treating B-cell diseases. It is hypothesised that the addition of Acalabrutinib to standard R-CHOP immunochemotherapy may improve the outcomes of patients with DLBCL.

### Who can participate?

Patients aged 16 years or older, with DLBCL

### What does the study involve?

Patients will be allocated to either Arm A, receiving R-CHOP immunochemotherapy alone, or Arm B, where they will receive R-CHOP immunochemotherapy in combination with Acalabrutinib. Both arms will receive a maximum of 6 cycles of treatment. Cycles will last 21 days. Those with an International Prognostic Index (IPI) of 0-1 will be randomly assigned a treatment arm, and those with an IPI of 2-5 will be automatically assigned to the R-CHOP Acalabrutinib combination arm.

At the end of the treatment phase, 3-8 weeks after they have received the last dose of R-CHOP medication, patients will attend an end-of-treatment visit for some tests.

What are the possible benefits and risks of participating?

Possible benefits:

1. The trial treatment may help to control your lymphoma
2. You will be helping to further our knowledge of how to treat cancer and this will benefit society and others with the same condition in the future

Possible risks/disadvantages:

1. The trial treatment may not control your lymphoma
2. There may be some unpleasant side effects
3. There could be risks to your child if you, or your partner, become pregnant, or begin breastfeeding
4. You may need to attend more clinic visits and provide more blood samples than if you were not taking part in the trial.

Where is the study run from?

Southampton General Hospital (UK)

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

September 2018 to October 2027

Who is funding the study?

AstraZeneca (UK)

Who is the main contact?

remodla@soton.ac.uk

## Contact information

### Type(s)

Scientific

### Contact name

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### Contact details

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## Additional identifiers

**ClinicalTrials.gov (NCT)**

NCT04546620

**Clinical Trials Information System (CTIS)**

2020-000998-25

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

266600

## **Central Portfolio Management System (CPMS)**

46717

### **Protocol serial number**

Grant Codes: ESR 19-20180

## **Study information**

### **Scientific Title**

A randomised phase II evaluation of molecular guided therapy for diffuse large B-cell lymphoma with acalabrutinib

### **Acronym**

REMoDL-A

### **Study objectives**

Diffuse large B-cell lymphoma (DLBCL) is the most common of the non-Hodgkin's lymphomas. Whilst the majority of patients will respond well to conventional treatment (R-CHOP a type of immunochemotherapy), a significant number of patients lymphoma will not respond to initial therapy or their disease will return after completion of therapy. In a number of B-cell diseases an enzyme called, Bruton tyrosine kinase (BTK) prevents death of tumour cells, including in DLBCL. Acalabrutinib is an orally active BTK-inhibitor and it is thought that stopping BTK being activated may help in treating B-cell diseases. It is hypothesised that the addition of Acalabrutinib to standard R-CHOP immunochemotherapy may improve outcomes of patients with DLBCL.

The main aims of this randomised phase II clinical study are:

- To determine if combining Acalabrutinib with R-CHOP improves efficacy, compared to R-CHOP alone, for the treatment of previously untreated patients with DLBCL.
- To compare progression-free survival, overall survival, event free survival, disease free survival, time to progression, response duration and overall response rate between both treatment and molecular groups.
- To assess differences in toxicity between the assigned treatments
- To assess differences in quality of life in different treatment arms
- To explore correlation of molecular characteristics in tumour material to clinical outcomes.
- To explore correlation of baseline PET features including metabolic tumour volume, tumour lesion glycolysis, extranodal sites and bone marrow involvement with clinical risk factor and molecular characteristics in tumour material.
- To compare metabolic response rates between molecular groups.

### **Ethics approval required**

Old ethics approval format

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

Approved 14/05/2021, South Central - Berkshire REC (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8222; berkshire.rec@hra.nhs.uk ), ref: 21/SC/0122

### **Study design**

Interventional randomized controlled trial

## Primary study design

Interventional

## Study type(s)

Treatment

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

Diffuse large B-cell lymphoma

## Interventions

Current interventions as of 30/01/2024:

Approximately 375 will be recruited to the clinical trial with 302 patients randomised to the experimental arm. Patients with an International Prognostic Index (IPI) of 0-1 will be randomised to a treatment arm 2:1 in favour of the experimental arm. Patients with an IPI of 2-5 will be allocated to the experimental arm without randomisation.

The study will be conducted in approximately 50 UK sites.

Patients will have histologically confirmed DLBCL, expressing CD20. Sufficient tumour material should be available to forward to a central laboratory for gene expression profiling and pathology review. Patients should have measurable disease of at least 15mm, previously untreated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent.

### Before Treatment:

The patient will be given information about the trial by the site team. The trial will be explained to them in detail by their physician and they will be given the opportunity to ask questions. The patient will be given a minimum of 24 hours before giving written informed consent.

After each patient has given informed consent, they will have a screening visit (this may be done over a period of days) where they will have a number of routine investigations to confirm their suitability for the trial.

### Intervention:

Patients recruited to the study will be randomised or assigned to either Arm A, receiving R-CHOP immunochemotherapy alone, or Arm B, where they will receive R-CHOP immunochemotherapy in combination with Acalabrutinib. Both arms will receive a maximum of 6 cycles of treatment. Cycles will last 21 days: the R-CHO infusion will be given on day 1; oral prednisolone will be self-administered on days 1-5 and Acalabrutinib capsules will be taken daily during cycles 2-6. Patients will also attend hospital during cycle 2 for an interim PET-CT scan.

### Drug Dose

Rituximab 375 mg/m<sup>2</sup>

Cyclophosphamide 750 mg/m<sup>2</sup>

Vincristine 1.4 mg/m<sup>2</sup> (max 2 mg)

Doxorubicin 50 mg/m<sup>2</sup>

Prednisolone 100 mg OD

Acalabrutinib (Arm B only) 100 mg BD

#### After treatment:

At the end of the treatment, 3-8 weeks after they have received the last dose of R-CHOP medication, patients will attend an end-of-treatment visit (this may be done over a period of days).

They will then go on to the follow-up phase of the trial. Patients will be followed up initially at 3 months, 6 months, 9 months, 12 months, 16 months, 20 months and 24 months. After 24 months, patients will be followed up yearly for progression, second-line therapy and survival data until 114 PFS events have been observed.

#### Previous interventions:

Up to 558 patients (453 randomised) will be recruited to the clinical trial with 302 patients randomised to the experimental arm and 151 to the control arm in a 2:1 randomisation.

The study will be conducted in approximately 50 UK sites.

Patients will have histologically confirmed DLBCL, expressing CD20. Sufficient tumour material should be available to forward to a central laboratory for gene expression profiling and pathology review. Patients should have measurable disease of at least 15mm, previously untreated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent.

#### Before Treatment:

The patient will be given information about the trial by the site team. The trial will be explained to them in detail by their physician and they will be given the opportunity to ask questions. The patient will be given a minimum of 24 hours before giving written informed consent.

After each patient has given informed consent, they will have a screening visit (this may be done over a period of days) where they will have a number of routine investigations to confirm their suitability for the trial.

#### Intervention:

Patients recruited to the study will be randomised to either Arm A, receiving R-CHOP immunochemotherapy alone, or Arm B, where they will receive R-CHOP immunochemotherapy in combination with Acalabrutinib. Both arms will receive a maximum of 6 cycles of treatment. Cycles will last 21 days: the R-CHO infusion will be given on day 1; oral prednisolone will be self-administered on days 1-5 and Acalabrutinib capsules will be taken daily during cycles 2-6. Patients will also attend hospital during cycle 2 for an interim PET-CT scan.

#### Drug Dose

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Acalabrutinib (Arm B only) 100 mg BD

#### After treatment:

At the end of the treatment, 3-8 weeks after they have received the last dose of R-CHOP medication, patients will attend an end-of-treatment visit (this may be done over a period of days).

They will then go on to the follow-up phase of the trial. Patients will be followed up initially at 3 months, 6 months, 9 months, 12 months, 16 months, 20 months and 24 months. After 24 months, patients will be followed up yearly for progression, second-line therapy and survival data until 114 PFS events have been observed.

## **Intervention Type**

Drug

## **Phase**

Phase II

## **Drug/device/biological/vaccine name(s)**

Rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone, acalabrutinib

## **Primary outcome(s)**

Progression-free survival at 2 years measured using patient records

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

1. To compare PFS between molecular groups. [ Time Frame: Last patient's last follow-up, approximately 4.5 years. ] PFS interaction with cell of origin phenotype (ABC, GCB and unclassifiable).
2. To compare PFS between treatment groups. [ Time Frame: Last patient's last follow-up, approximately 4.5 years. ] PFS interaction with clinical variables, including for example IPI, bulk, components of IPI, age and others to be determined in the SAP.
3. To compare overall survival (OS) between both treatment and molecular groups. [ Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience an OS event will be censored at the date of last follow-up. ] Overall survival (OS), defined as time from registration to death from any cause.
4. To compare event free survival (EFS) between both treatment and molecular groups. [ Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience an EFS event will be censored at the date of last follow-up. ] Event-free survival (EFS), or time to treatment failure, defined as time from registration to any treatment failure including disease progression, or discontinuation of treatment for any reason.
5. To compare disease free survival (DFS) between both treatment and molecular groups. [ Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience a DFS event will be censored at the date of last follow-up. ] Disease-free survival (DFS), defined as time of documentation of disease-free state to disease recurrence or death as a result of lymphoma or acute toxicity of treatment.
6. To compare time to progression (TTP) between both treatment and molecular groups. [ Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience a TTP event will be censored at the date of last follow-up. ] Time to progression (TTP), defined as time from registration until documented lymphoma progression or death as a result of lymphoma. Deaths from other causes are censored at the time of death.
7. To compare duration of response (DoR) between both treatment and molecular groups. [ Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience a RD event will be censored at the date of last follow-up. ] Response duration (DoR), defined as the time from documentation of response until the documentation of relapse or progression.
8. To compare overall response rate (ORR) and complete response rate (CR) between both treatment groups. [ Time Frame: Complete and overall response rates, as recorded at the end of treatment (up to 21 weeks) . ] Assessment using the Lugano Response Criteria for Malignant

Lymphoma.

9. To assess differences in toxicity between assigned treatments. [ Time Frame: At all visits up to 24 months follow-up. ] Evaluation of toxicity according to CTCAE version 5.

10. To assess differences in quality of life between treatment arms. [ Time Frame: At baseline, cycle 2 day 1, cycle 3 day 1, cycle 5 day 1, end of treatment and at 3, 6, 12, 20 and 24 month follow-ups. Each cycle is 21 days. ] Application of the EORTC QLQ-C30 and FACT-Lym questionnaires.

### **Completion date**

31/10/2027

## **Eligibility**

### **Key inclusion criteria**

Current inclusion criteria as of 30/01/2024:

1. Histologically confirmed DLBCL, expressing CD20. Sufficient diagnostic material should be available to forward to HMDS for gene expression profiling and central pathology review. The following diagnoses by 2016 WHO classification of lymphoid neoplasms may be included:
  - 1.1. DLBCL, not otherwise specified (NOS)
  - 1.2. T-cell/histiocyte-rich large B-cell lymphoma
  - 1.3. Epstein-Barr virus positive DLBCL, NOS
  - 1.4. ALK-positive large B-cell lymphoma
  - 1.5 HHV8-positive DLBCL, NOS
  - 1.6. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma)
  - 1.7. High-grade B-cell lymphoma, NOS
2. At least one bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension.
3. Not previously treated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent
4. Stage IAX (bulk defined as lymph node mass [either single or conglomerate] diameter >7.5cm) to stage IV disease and deemed to require a full course of chemotherapy. Patients with non-bulky IE disease will not be eligible.
5. ECOG performance status 0-2 or 3 if this is directly attributable to lymphoma.
6. Adequate bone marrow function with platelets >100x10<sup>9</sup>/L; neutrophils >1.0x10<sup>9</sup>/L prior to cycle 1 treatment, unless lower figures are attributable to lymphoma.
7. Measured or calculated creatinine clearance >30mls/min, (calculated using the formula of Cockcroft and Gault [(140-Age) x Mass (kg) x (1.04 (for women) or 1.23 (for men))/Serum Creatinine (µmolL)]).
8. Serum bilirubin ≤35µmol/L and transaminases (AST or ALT) <1.5x upper limit of normal prior to cycle 1 treatment.
9. Cardiac function sufficient to tolerate 300mg/m<sup>2</sup> of doxorubicin. A pre-treatment echocardiogram or MUGA is required to establish baseline LVEF equal to or greater than institutional normal range.
10. No concurrent uncontrolled medical condition.
11. Life expectancy >3 months.
12. Aged 16 years or above.
13. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
14. Ability to understand the purpose and risks of the study and provide signed and dated informed consent.

**Previous inclusion criteria:**

1. Histologically confirmed DLBCL, expressing CD20. Sufficient diagnostic material should be available to forward to HMDS for gene expression profiling and central pathology review. The following diagnoses by 2016 WHO classification of lymphoid neoplasms may be included:
  - 1.1. DLBCL, not otherwise specified (NOS)
  - 1.2. T-cell/histiocyte-rich large B-cell lymphoma
  - 1.3. Epstein-Barr virus positive DLBCL, NOS
  - 1.4. ALK-positive large B-cell lymphoma
  - 1.5 HHV8-positive DLBCL, NOS
  - 1.6. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma)
  - 1.7. High-grade B-cell lymphoma, NOS
2. At least one bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension as measured by CT
3. Not previously treated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent
4. Stage IAX (bulk defined as lymph node mass [either single or conglomerate] diameter >7.5cm) to stage IV disease and deemed to require a full course of chemotherapy. Patients with non-bulky IE disease will not be eligible.
5. ECOG performance status 0-2 or 3 if this is directly attributable to lymphoma.
6. Adequate bone marrow function with platelets >100x10<sup>9</sup>/L; neutrophils >1.0x10<sup>9</sup>/L at study entry, unless lower figures are attributable to lymphoma.
7. Measured or calculated creatinine clearance >30mls/min, (calculated using the formula of Cockcroft and Gault [(140-Age) x Mass (kg) x (1.04 (for women) or 1.23 (for men))/Serum Creatinine (µmolL)]).
8. Serum bilirubin <35µmol/L and transaminases <1.5x upper limit of normal at time of study entry.
9. Cardiac function sufficient to tolerate 300mg/m<sup>2</sup> of doxorubicin. A pre-treatment echocardiogram or MUGA is required to establish baseline LVEF equal to or greater than institutional normal range.
10. No concurrent uncontrolled medical condition.
11. Life expectancy >3 months.
12. Aged 16 years or above.
13. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
14. Ability to understand the purpose and risks of the study and provide signed and dated informed consent.

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

16 years

**Sex**

All

## Total final enrolment

294

### Key exclusion criteria

Current exclusion criteria as of 30/01/2024:

1. Previous history of treated or untreated indolent lymphoma. Newly diagnosed patients with DLBCL found to have small cell infiltration of the bone marrow or other diagnostic material (discordant lymphoma) will be eligible.
2. Patients who have received immunisation with a live vaccine within four weeks prior to enrolment will be ineligible.
3. Diagnosis of primary mediastinal lymphoma.
4. Diagnosis of primary Central Nervous System lymphoma or secondary CNS involvement.
5. History of stroke or intracranial haemorrhage in preceding 6 months.
6. History of bleeding diathesis (e.g. haemophilia, von Willebrand disease).
7. History of drug-specific hypersensitivity or anaphylaxis to any study drug (including active product or excipient components).
8. Requires or receiving anticoagulation with warfarin or equivalent antagonists (e.g. phenprocoumon) within 7 days of first dose of acalabrutinib. Patients using therapeutic low molecule weight heparin or low dose aspirin will be eligible, as will those receiving direct oral anticoagulants.
9. Prior exposure to an inhibitor in the BCR pathway (e.g. Btk inhibitors, phosphoinositide-3 kinase (PI3K), or Syk inhibitors) or BCL-2 inhibitor (e.g. ABT-199).
10. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
11. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Patients receiving proton pump inhibitors should switch to short-acting H2-receptor antagonists or antacids prior to the commencement of acalabrutinib, if randomised to receive acalabrutinib.
12. Active significant infection (e.g. progressive multifocal leukoencephalopathy (PML), tuberculosis, sepsis, and opportunistic infections).
13. Uncontrolled autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP).
14. Major surgery in the preceding 4 weeks of first dose of Acalabrutinib (if applicable).
15. Corticosteroid use >30 mg/day of prednisone or equivalent, for purposes other than for lymphoma symptom control. Patients receiving corticosteroid treatment with <30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to the start of Cycle 1. If glucocorticoid treatment is urgently required for lymphoma symptom control, this may be delivered in the 28 days prior to initiating therapy, with no maximum dose.
16. Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, NYHA Class II or greater congestive heart failure, cerebrovascular accident or transient ischemic attack.
17. Serological positivity for Hepatitis B, C, or known HIV infection.
  - a. Positive test results for chronic HBV infection (defined as positive HBsAg serology) will not be eligible. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) will not be eligible. Patients who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible.
  - b. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
18. Men who can father children must agree to use one highly effective form of contraception

with additional barrier or abstinence during the study and for 12 months after the last treatment dose.

19. Breastfeeding or pregnant women.

20. Men who can father children must agree to use two highly effective forms of contraception with additional barrier or abstinence during the study and for 12 months after the last treatment dose.

21. Men must agree to refrain from sperm donation during the study and for 12 months after the last treatment dose.

22. Serious medical or psychiatric illness likely to affect participation or that may compromise the ability to give informed consent.

23. Prior malignancy (other than DLBCL), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for  $\geq 2$  years or which will not limit survival to  $< 2$  years.

24. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease, resection of the stomach or small bowel, partial or complete bowel obstruction or gastric restrictions and bariatric surgery, such as gastric bypass that would limit absorption of oral medication.

25. Any immunotherapy within 4 weeks of 1st dose.

26. Concurrent participation in another therapeutic clinical trial.

27. History of pneumonitis.

Previous exclusion criteria from 11/05/2023 to 30/01/2024:

1. Previous history of treated or untreated indolent lymphoma. Newly diagnosed patients with DLBCL found to have small cell infiltration of the bone marrow or other diagnostic material (discordant lymphoma) will be eligible.

2. Patients who have received immunisation with a live vaccine within four weeks prior to enrolment will be ineligible.

3. Diagnosis of primary mediastinal lymphoma.

4. Diagnosis of primary Central Nervous System lymphoma or secondary CNS involvement.

5. History of stroke or intracranial haemorrhage in preceding 6 months.

6. History of bleeding diathesis (e.g. haemophilia, von Willebrand disease).

7. History of drug-specific hypersensitivity or anaphylaxis to any study drug (including active product or excipient components).

8. Requires or receiving anticoagulation with warfarin or equivalent antagonists (e.g. phenprocoumon) within 7 days of first dose of acalabrutinib. Patients using therapeutic low molecule weight heparin or low dose aspirin will be eligible, as will those receiving direct oral anticoagulants.

9. Prior exposure to an inhibitor in the BCR pathway (e.g. Btk inhibitors, phosphoinositide-3 kinase (PI3K), or Syk inhibitors) or BCL-2 inhibitor (e.g. ABT-199).

10. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.

11. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Patients receiving proton pump inhibitors should switch to short-acting H2-receptor antagonists or antacids prior to the commencement of acalabrutinib, if randomised to receive acalabrutinib.

12. Active significant infection (e.g. progressive multifocal leukoencephalopathy (PML), tuberculosis, sepsis, and opportunistic infections).

13. Uncontrolled autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP).

14. Major surgery in the preceding 4 weeks of first dose of Acalabrutinib (if applicable).

15. Corticosteroid use  $>30$  mg/day of prednisone or equivalent, for purposes other than for lymphoma symptom control. Patients receiving corticosteroid treatment with  $<30$  mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks'

duration prior to the start of Cycle 1. If glucocorticoid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, prednisone 100 mg or equivalent could be given for a maximum of 14 days as a prephase. A dose of upto 30mg or prenisolone or equivalent may be used during the screening phase to control symptoms.

16. Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, NYHA Class II or greater congestive heart failure, cerebrovascular accident or transient ischemic attack.

17. Serological positivity for Hepatitis B, C, or known HIV infection.

a. Positive test results for chronic HBV infection (defined as positive HBsAg serology) will not be eligible. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) will not be eligible. Patients who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible.

b. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

18. Men who can father children must agree to use one highly effective form of contraception with additional barrier or abstinence during the study and for 12 months after the last treatment dose.

19. Breastfeeding or pregnant women.

20. Men who can father children must agree to use two highly effective forms of contraception with additional barrier or abstinence during the study and for 12 months after the last treatment dose.

21. Men must agree to refrain from sperm donation during the study and for 12 months after the last treatment dose.

22. Serious medical or psychiatric illness likely to affect participation or that may compromise the ability to give informed consent.

23. Prior malignancy (other than DLBCL), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for  $\geq 2$  years or which will not limit survival to  $< 2$  years.

24. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease, resection of the stomach or small bowel, partial or complete bowel obstruction or gastric restrictions and bariatric surgery, such as gastric bypass that would limit absorption of oral medication.

25. Any immunotherapy within 4 weeks of 1st dose.

26. Concurrent participation in another therapeutic clinical trial.

27. History of pneumonitis.

Original exclusion criteria:

1. Previous history of treated or untreated indolent lymphoma. Newly diagnosed patients with DLBCL found to have small cell infiltration of the bone marrow or other diagnostic material (discordant lymphoma) will be eligible.

2. Patients who have received immunisation with a live vaccine within four weeks prior to enrolment will be ineligible.

3. Diagnosis of primary mediastinal lymphoma.

4. Diagnosis of primary Central Nervous System lymphoma or secondary CNS involvement.

5. History of stroke or intracranial haemorrhage in preceding 6 months.

6. History of bleeding diathesis (e.g. haemophilia, von Willebrand disease).

7. History of drug-specific hypersensitivity or anaphylaxis to any study drug (including active product or excipient components).

8. Requires or receiving anticoagulation with warfarin or equivalent antagonists (e.g. phenprocoumon) within 7 days of first dose of acalabrutinib. Patients using therapeutic low molecule weight heparin or low dose aspirin will be eligible, as will those receiving direct oral anticoagulants.

9. Prior exposure to an inhibitor in the BCR pathway (e.g. Btk inhibitors, phosphoinositide-3 kinase (PI3K), or Syk inhibitors) or BCL-2 inhibitor (e.g. ABT-199).
10. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
11. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
12. Active significant infection (e.g. progressive multifocal leukoencephalopathy (PML), tuberculosis, sepsis, and opportunistic infections).
13. Uncontrolled autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP).
14. Major surgery in the preceding 4 weeks of first dose of study drug.
15. Corticosteroid use >30 mg/day of prednisone or equivalent, for purposes other than for lymphoma symptom control. Patients receiving corticosteroid treatment with <30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to the start of Cycle 1. If glucocorticoid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, prednisone 100 mg or equivalent could be given for a maximum of 14 days as a prephase. A dose of upto 30mg or prednisolone or equivalent may be used during the screening phase to control symptoms.
16. Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, NYHA Class II or greater congestive heart failure, cerebrovascular accident or transient ischemic attack.
17. Serological positivity for Hepatitis B, C, or known HIV infection.
  - a. Positive test results for chronic HBV infection (defined as positive HBsAg serology) will not be eligible. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) will not be eligible. Patients who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible.
  - b. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
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19. Breastfeeding or pregnant women.
20. Men who can father children must agree to use two highly effective forms of contraception with additional barrier or abstinence during the study and for 12 months after the last treatment dose.
21. Men must agree to refrain from sperm donation during the study and for 12 months after the last treatment dose.
22. Serious medical or psychiatric illness likely to affect participation or that may compromise the ability to give informed consent.
23. Prior malignancy (other than DLBCL), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for  $\geq 2$  years or which will not limit survival to  $< 2$  years.
24. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease, resection of the stomach or small bowel, partial or complete bowel obstruction or gastric restrictions and bariatric surgery, such as gastric bypass that would limit absorption of oral medication.
25. Any immunotherapy within 4 weeks of 1st dose.
26. Concurrent participation in another therapeutic clinical trial.
27. History of pneumonitis.

**Date of first enrolment**

19/10/2021

**Date of final enrolment**

30/06/2025

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

United Kingdom

England

Scotland

Wales

**Study participating centre****Southampton General Hospital**

Tremona Road

Southampton

United Kingdom

SO16 6YD

**Study participating centre****Churchill Hospital**

Churchill Hospital

Old Road

Headington

Oxford

United Kingdom

OX3 7LE

**Study participating centre****Beatson West of Scotland Cancer Centre**

1053 Great Western Road

Glasgow

United Kingdom

G12 0YN

**Study participating centre****Colchester General Hospital**

Colchester District General Hosp.

Charter Way

Turner Road

Colchester

United Kingdom  
CO4 5JL

**Study participating centre**

**Queen's Hospital**

Rom Valley Way  
Romford  
United Kingdom  
RM7 0AG

**Study participating centre**

**Freeman Hospital**

Newcastle Upon Tyne Hospital Trust  
Freeman Road  
High Heaton  
Newcastle  
United Kingdom  
NE7 7DN

**Study participating centre**

**Victoria Hospital**

Whinney Heys Road  
Blackpool  
United Kingdom  
FY3 8NR

**Study participating centre**

**Royal Cornwall Hospital (treliske)**

Treliske  
Truro  
United Kingdom  
TR1 3LJ

**Study participating centre**

**Nottingham City Hospital**

Hucknall Road  
Nottingham  
United Kingdom  
NG5 1PB

**Study participating centre**

**Chase Farm Hospital**

127 the Ridgeway

Enfield

United Kingdom

EN2 8JL

**Study participating centre**

**East Kent Hospitals University NHS Foundation Trust**

Kent & Canterbury Hospital

Ethelbert Road

Canterbury

United Kingdom

CT1 3NG

**Study participating centre**

**Ipswich Hospital**

Heath Road

Ipswich

United Kingdom

IP4 5PD

**Study participating centre**

**Torbay Hospital**

Newton Road

Torquay

United Kingdom

TQ2 7AA

**Study participating centre**

**St James' University Hospital**

Beckett Street

Leeds

United Kingdom

LS9 7TF

**Study participating centre**

**Lewisham and Greenwich NHS Trust**

University Hospital Lewisham

Lewisham High Street

London  
United Kingdom  
SE13 6LH

**Study participating centre**  
**Milton Keynes University Hospital NHS Foundation Trust**  
Standing Way  
Eaglestone  
Milton Keynes  
United Kingdom  
MK6 5LD

**Study participating centre**  
**NHS Lanarkshire**  
14 Beckford Street  
Hamilton  
United Kingdom  
ML3 0TA

**Study participating centre**  
**Norfolk and Norwich University Hospitals NHS Foundation Trust**  
Colney Lane  
Colney  
Norwich  
United Kingdom  
NR4 7UY

**Study participating centre**  
**Derriford Hospital**  
University Hospitals Plymouth NHS Trust  
Derriford Road  
Derriford  
Plymouth  
United Kingdom  
PL6 8DH

**Study participating centre**  
**The Maidstone Hospital**  
Maidstone and Tunbridge Wells NHS Trust  
Hermitage Lane  
Maidstone

United Kingdom  
ME16 9QQ

**Study participating centre**  
**Royal Bournemouth Hospital**  
Castle Lane East  
Bournemouth  
United Kingdom  
BH7 7DW

**Study participating centre**  
**Royal Devon and Exeter Hospital**  
Royal Devon & Exeter Hospital  
Barrack Road  
Exeter  
United Kingdom  
EX2 5DW

**Study participating centre**  
**University College London Hospitals NHS Foundation Trust**  
250 Euston Road  
London  
United Kingdom  
NW1 2PG

**Study participating centre**  
**University Hospitals Sussex NHS Foundation Trust**  
Worthing Hospital  
Lyndhurst Road  
Worthing  
United Kingdom  
BN11 2DH

**Study participating centre**  
**Leicester Royal Infirmary**  
University Hospitals of Leicester NHS Trust  
Infirmary Square  
Leicester  
United Kingdom  
LE1 5WW

**Study participating centre**  
**The Christie NHS Foundation Trust**  
550 Wilmslow Road  
Withington  
Manchester  
United Kingdom  
M20 4BX

**Study participating centre**  
**Queen Alexandra Hospital**  
Portsmouth Hospitals NHS Trust  
Southwick Hill Road  
Cosham  
Portsmouth  
United Kingdom  
PO6 3LY

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

**Study participating centre**  
**Poole Hospital**  
University Hospitals Dorset NHS Foundation Trust  
Longfleet Road  
Poole  
United Kingdom  
BH15 2JB

**Study participating centre**  
**Swansea Bay University Local Health Board**  
One Talbot Gateway  
Seaway Drive  
Seaway Parade  
Industrial Estate  
Baglan

Port Talbot  
United Kingdom  
SA12 7BR

**Study participating centre**  
**Chelsea and Westminster Hospital NHS Foundation Trust**  
Chelsea & Westminster Hospital  
369 Fulham Road  
London  
United Kingdom  
SW10 9NH

**Study participating centre**  
**Broomfield Hospital**  
Court Road  
Broomfield  
Chelmsford  
United Kingdom  
CM1 7ET

**Study participating centre**  
**Southend Hospital**  
Prittlewell Chase  
Westcliff-on-sea  
United Kingdom  
SS0 0RY

**Study participating centre**  
**Darent Valley Hospital**  
Darenth Wood Road  
Dartford  
United Kingdom  
DA2 8DA

**Study participating centre**  
**James Cook University Hospital**  
Marton Road  
Middlesbrough  
United Kingdom  
TS4 3BW

**Study participating centre**  
**United Lincolnshire Hospitals NHS Trust**  
Lincoln County Hospital  
Greetwell Road  
Lincoln  
United Kingdom  
LN2 5QY

**Study participating centre**  
**Bolton Royal Hospital**  
Minerva Road  
Farnworth  
Bolton  
United Kingdom  
BL4 0JR

**Study participating centre**  
**Sandwell General Hospital**  
Lyndon  
West Bromwich  
United Kingdom  
B71 4HJ

**Study participating centre**  
**Harrogate District Hospital**  
Lancaster Park Road  
Harrogate  
United Kingdom  
HG2 7SX

**Study participating centre**  
**Addenbrookes**  
Addenbrookes Hospital  
Hills Road  
Cambridge  
United Kingdom  
CB2 0QQ

**Study participating centre**

**South Warwickshire University NHS Foundation Trust**

Warwick Hospital  
Lakin Road  
Warwick  
United Kingdom  
CV34 5BW

**Study participating centre**

**The Royal Oldham Hospital**

Rochdale Road  
Oldham  
United Kingdom  
OL1 2JH

**Study participating centre**

**Stoke Mandeville Hospital**

Mandeville Road  
Aylesbury  
United Kingdom  
HP21 8AL

**Study participating centre**

**Wycombe Hospital**

Queen Alexandra Road  
High Wycombe  
United Kingdom  
HP11 2TT

**Study participating centre**

**Hampshire Hospitals NHS Foundation Trust**

Basingstoke and North Hampshire Hos  
Aldermaston Road  
Basingstoke  
United Kingdom  
RG24 9NA

**Study participating centre**

**University Hospitals Coventry and Warwickshire NHS Trust**

Walsgrave General Hospital  
Clifford Bridge Road  
Coventry

United Kingdom  
CV2 2DX

**Study participating centre**  
**Royal United Hospital**  
Combe Park  
Bath  
United Kingdom  
BA1 3NG

**Study participating centre**  
**West Suffolk Hospital**  
Hardwick Lane  
Bury St. Edmunds  
United Kingdom  
IP33 2QZ

## Sponsor information

**Organisation**  
University Hospital Southampton NHS Foundation Trust

**ROR**  
<https://ror.org/0485axj58>

## Funder(s)

**Funder type**  
Industry

**Funder Name**  
AstraZeneca

**Alternative Name(s)**  
AstraZeneca PLC, Pearl Therapeutics, AZ

**Funding Body Type**  
Government organisation

**Funding Body Subtype**

For-profit companies (industry)

## Location

United Kingdom

# Results and Publications

## Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date.

## IPD sharing plan summary

Data sharing statement to be made available at a later date

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes