

# A phase I trial for patients with a type of myelofibrosis, which aims to determine the recommended phase II dose of the drug PLX2853 when it is combined with a drug the patient is already on, ruxolitinib. This trial is for patients who are not receiving an adequate disease response from just ruxolitinib

<b>Submission date</b> 17/11/2020	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 17/11/2020	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 06/01/2026	<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

Also see: <https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-plx2853-with-ruxolitinib-for-myelofibrosis-promise>

### Background and study aims

Myelofibrosis (MF) is a cancer of the bone marrow that disrupts the production of blood cells. Symptoms of MF include anaemia (low red cell levels), weakness, tiredness and often an enlarged spleen. Standard treatment can involve chemotherapy, radiotherapy, a stem cell transplant or treatment with a drug called ruxolitinib. Ruxolitinib targets the specific cells that play a part in the development of MF, and is the only drug licenced to treat MF. Previous research has shown that ruxolitinib is good at reducing symptoms of MF and decreasing the size of the spleen. However, the majority of patients do not show a complete response to ruxolitinib, meaning that another treatment needs to be added to ruxolitinib to improve the outcome for patients. This study will test whether combining ruxolitinib with another drug called a bromodomain and extra terminal inhibitor (BETi) is safe for MF. Research has suggested that combining these two drugs will have a clinical benefit to patients. The main aims of the study are to find a suitable dose of PLX2853 when combined with ruxolitinib, and investigate the safety by looking at the side effects of treatment, and to see how well the combination treats MF.

### Who can participate?

The PROMise trial is for patients diagnosed with intermediate-2 or high risk myelofibrosis currently being treated with ruxolitinib, who may benefit from a new drug, PLX2853, being added to their ruxolitinib.

### What does the study involve?

Patients will then take both drugs in oral tablet form (PLX2853 and ruxolitinib) every day for up to 8 cycles of treatment, each cycle lasting 21 days. If at the end of 8 cycles the study doctor feels it is helping the patient and they are not experiencing any major side effects, it will be possible to continue with further cycles of treatment. The patient will visit the hospital for blood tests, physical assessments and a further bone marrow biopsy throughout the trial. More detail of these assessments can be found in the Patient Information Sheet.

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

The possible benefit is that adding PLX2853 to ruxolitinib could further reduce the size of the patient's spleen and modify the natural history of the myelofibrosis. PLX2853 is not chemotherapy, but works by targeting specific cells that are involved in the development and progression of myelofibrosis. PLX2853 works by targeting and slowing down certain activities within cells that promote tumour growth. By inhibiting these activities, PLX2853 may help to stabilise or reduce the growth of tumour cells.

Patients will have to have bone marrow aspirate and biopsy procedures performed whether or not they enter the PROMise trial. This may be painful, uncomfortable afterwards and may cause a small amount of bleeding.

Having blood samples taken may cause some discomfort, bleeding or bruising where the needle enters the body and, in rare cases, light-headedness and fainting.

There are possible side effects from both PLX2853 and ruxolitinib, which are documented in the Patient Information Sheet. There may be risks or side effects of the study drugs that are unknown at this time.

### Where is the study run from?

The University of Birmingham (UK)

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

May 2019 to July 2026

### Who is funding the study?

Cancer Research UK

### Who is the main contact?

Prof. Adam Mead (scientific), [adam.mead@imm.ox.ac.uk](mailto:adam.mead@imm.ox.ac.uk)

## Contact information

### Type(s)

Scientific

### Contact name

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**Additional identifiers**

**Clinical Trials Information System (CTIS)**

2019-000916-27

**Integrated Research Application System (IRAS)**

261523

**ClinicalTrials.gov (NCT)**

Nil known

**Protocol serial number**

CPMS 46423, IRAS 261523

## Study information

### Scientific Title

Investigation into the combination of PLX2853 with ruxolitinib in patients with intermediate-2 or high risk myelofibrosis not receiving an adequate response with ruxolitinib alone

### Acronym

PROMise

### Study objectives

PROMise is a phase I multicentre trial which aims to determine the recommended phase II dose (RP2D) of PLX2853 in combination with ruxolitinib using a continual reassessment method (CRM) design

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

Approved 03/11/2020, East Midlands – Leicester Central REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44(0)207 104 8388; leicestercentral.rec@hra.nhs.uk), ref: 20/EM/0235

### Study design

Non-randomized; Interventional; Design type: Treatment, Drug

### Primary study design

Interventional

### Study type(s)

Treatment

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

Myelofibrosis

### Interventions

This is a multicentre phase I dose finding study for PLX2853 when administered in combination with ruxolitinib in patients with high risk or Intermediate-2 myelofibrosis.

Patients who consent to participate will have a screening period of up to 28 days before trial registration for the following assessments to take place. The patient will have a clinical and physical exam (including vital signs, height and weight), blood tests, an ECG, palpation and ultrasound of the spleen, and bone marrow aspirate. Patients will also be asked to complete a few optional Quality of Life questionnaires.

Once registered to the study, patients will receive up to 8 cycles of ruxolitinib and PLX2853 combination therapy orally daily, with each cycle lasting 21 days. At the end of 8 cycles, patients experiencing clinical benefit may continue on trial treatment.

Patients will be seen on the day 1 of cycles 1-8 for a clinical and physical assessment, as well as for blood tests, spleen palpation and quality of life questionnaires. On day 8 and day 15 of cycle 1, and day 15 of cycle 2-4 there will be additional blood tests, with an ECG done on day 15 of cycle 4 if clinically indicated. On day 1 of cycle 5 there will be an ultrasound of the spleen and a disease response assessment, in addition to the assessments previously mentioned. On day 15 of cycle 8 there will be an ECG (if clinically indicated), as well as blood tests, ultrasound and palpation of the spleen, disease response assessment, bone marrow aspirate and trephine and MF-SAF questionnaire.

If the patient continues treatment after 8 cycles, they will be assessed every 4 cycles with a clinical and physical assessment, blood tests and quality of life questionnaires. With an ultrasound and palpation of the spleen, and disease response assessment done every 8 cycles.

Once the patient has completed treatment they will have a visit 28 days after this. This visit will include clinical and physical assessment and blood tests. After this they will be followed up annually, this will include a clinical and physical assessment, blood tests, palpation of the spleen, quality of life questionnaires, and an optional bone marrow aspirate.

## **Intervention Type**

Drug

## **Phase**

Phase I

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

PLX2853, ruxolitinib

## **Primary outcome(s)**

1. The RP2D of PLX2853 administered in combination with ruxolitinib that is safe and tolerable is measured using the occurrence of a dose limiting toxicity (DLT) in the first cycle (21 days)
2. The efficacy of the combination of PLX2853 and ruxolitinib for reduction in spleen size is measured using a reduction in palpable spleen length of >50% from screening to end of 8 cycles of treatment

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

1. The safety of the combination of PLX2853 and ruxolitinib is measured using the incidence of adverse events (recorded using Common Terminology Criteria for Adverse Events (CTCAE) v4.0, from commencement of protocol treatment to 28 days post treatment discontinuation
2. The effect of the combination of PLX2853 and ruxolitinib on myelofibrosis-associated symptoms is measured using the proportion of patients whose ruxolitinib dose was adjusted following administration of PLX2853 and total symptom score assessed by the Myelofibrosis Symptom Assessment Form (MFSAF) after 4 and 8 cycles
3. The effect of the combination of PLX2853 and ruxolitinib on bone marrow fibrosis is measured using the bone marrow fibrosis assessed via bone marrow samples after 8 cycles
4. Overall haematological response is measured using the overall response after 8 cycles of treatment assessed using International Working Group (IWG) Criteria, where response includes

Complete Response (CR) and Partial Response (PR). Anaemia response using International Working Group (IWG) Criteria and rate of red blood cell (RBC) transfusion

5. Overall survival time is measured using the overall survival time defined as the time from date of registration to date of death from any cause

6. Leukaemia-free time is measured using the leukaemia free survival time, defined as the time from date of registration to earliest of date of death or date of progression to leukaemia

7. Progression free survival is measured using the progression-free survival time, defined as the time from date of registration to the earlier of the date of death from any cause or disease progression by the IWG Criteria

### **Completion date**

31/07/2026

## **Eligibility**

### **Key inclusion criteria**

1. Age  $\geq 16$  years
2. Primary or secondary myelofibrosis OR Dynamic International Prognostic Scoring System (DIPSS) defined risk groups intermediate-2 or high risk
3. Treated with  $\geq 24$  weeks of ruxolitinib with ongoing residual splenomegaly  $> 5$ cm from costal margin
4. Platelets  $> 75 \times 10^9/L$
5. Neutrophils  $> 1.0 \times 10^9/L$
6.  $< 10\%$  blasts in peripheral blood and/or bone marrow
7. Coagulation (INR or PT) and Activated partial thromboplastin time  $\leq 1.5 \times ULN$
8. Albumin  $> 3.0$  g/dL
9. Stable dose of ruxolitinib (no dose modifications) established for 4 weeks prior to trial entry
10. Except as specified above for organ function, all drug-related toxicity from previous therapy for myelofibrosis must be resolved (to Grade  $\leq 1$  or baseline per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [NCI CTCAE v4.0]) prior to study treatment administration (Grade 2: alopecia, hot flashes, decreased libido, or neuropathy is allowed)
11. Able to provide written informed consent
12. Able to comply with trial treatment and follow-up
13. Serum total bilirubin  $\leq 2.0 \times ULN$  OR Direct bilirubin  $\leq ULN$  for patients with total bilirubin  $> 2.0 \times ULN$ 
  - 13.1. Exception for elevated total bilirubin secondary to Gilbert's disease, in which case it must be  $\leq 3 \times ULN$
14. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.0 \times ULN$

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Mixed

### **Lower age limit**

16 years

## Upper age limit

110 years

## Sex

All

## Total final enrolment

0

## Key exclusion criteria

1. Prior exposure to a bromodomain inhibitor such as OTX-015 or CPI-0610
2. Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to trial entry)
3. Patients and partners of childbearing potential (pre-menopausal female capable of becoming pregnant) not willing to use effective contraception from the time of negative pregnancy test during screening to 90 days after the last dose of study drug
4. Women of non-child-bearing potential may be included if they are either surgically sterile or have been postmenopausal for  $\geq 1$  year
5. Ongoing systemic infection requiring treatment with antibiotic, antiviral, or antifungal treatment
6. ECOG Performance Status Score  $\geq 3$
7. Clinically significant cardiac disease, defined as any of the following:
  - 7.1. Clinically significant cardiac arrhythmias including bradyarrhythmias and/or patients who require anti-arrhythmic therapy (excluding beta blockers or digoxin). Patients with controlled atrial fibrillation are not excluded
  - 7.2. Congenital long QT syndrome or patients taking concomitant medications known to prolong the QT interval (drugs with a low risk of QTc prolongation that are needed for infection control or nausea may be permitted with approval from the Clinical Coordinator)
  - 7.3. QT interval corrected for heart rate using the Fridericia method (QTcF)  $\geq 450$  msec males or QTcF  $\geq 470$  msec (females) at Screening
  - 7.4. History of clinically significant cardiac disease or congestive heart failure  $>$  New York Heart Association Class II. Patients must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or myocardial infarction within the past 6 months
  - 7.5. Uncontrolled hypertension, defined as systolic blood pressure  $> 160$  mmHg or diastolic blood pressure  $> 100$  mmHg which has been confirmed by 2 successive measurements despite optimal medical management
  - 7.6. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within the 3 months before start of study medication (except for adequately treated catheter-related venous thrombosis occurring  $> 1$  month before the start of study medication)
8. Inadequate renal function as defined by eGFR or CrCl  $\leq 30$  mls/min
9. Current active viral hepatitis including hepatitis A (hepatitis A virus immunoglobulin M positive), hepatitis B (hepatitis B virus [HBV] surface antigen positive), or hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid). Patients with HCV with undetectable virus after treatment are eligible. Patients with a prior history of HBV are eligible if quantitative PCR for HBV DNA is negative. Note that elevated levels of biotin may interfere with viral serology testing
10. Use of biotin (i.e., Vitamin B7) or supplements containing biotin higher than the daily adequate intake of 30  $\mu\text{g}$  (NIH 2020) (Note: Patients who switch from a high dose to a dose of 30  $\mu\text{g}$ /day or less are eligible for study entry.)

11. Known or suspected allergy to the investigational agent or any agent given in association with this study

12. Inability to take oral medication or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the Investigator, would preclude adequate absorption

13. Patient is participating in any other therapeutic clinical study (observational or registry studies are allowed)

**Date of first enrolment**

15/11/2020

**Date of final enrolment**

30/06/2025

## **Locations**

**Countries of recruitment**

United Kingdom

England

Northern Ireland

Wales

**Study participating centre**

**Cardiff and Vale University Health Board**

Cardiff and Vale UHB Headquarters

University Hospital of Wales (UHW)

Heath Park

Cardiff

Cardiff

Wales

CF14 4XW

**Study participating centre**

**Southampton General Hospital**

University of Southampton and University Hospital Southampton NHS Foundation Trust

Tremona Road

Southampton

England

SO16 6YD

**Study participating centre**

**St Thomas's Hospital**

Guy's and St Thomas' NHS Foundation Trust  
249 Westminster Bridge Road  
London  
England  
SE1 7EH

**Study participating centre****Cambridge Biomedical Campus**

Cambridge University Hospitals NHS Foundation Trust  
Hills Road  
Cambridge  
England  
CB2 0QQ

**Study participating centre****Belfast Health & Social Care Trust**

Knockbracken Healthcare Park  
Saintfield Road  
Belfast  
Northern Ireland  
BT8 8BH

**Study participating centre****The Christie Hospital**

The Christie NHS Foundation Trust  
Wilmslow Road  
Withington  
Manchester  
England  
M20 4BX

**Study participating centre****St Mary's Hospital**

Imperial College Healthcare NHS Trust  
South Wharf Road  
London  
England  
W2 1BL

**Study participating centre**

**Freeman Hospital**

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

**Study participating centre****Leicester Royal Infirmary**

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**Study participating centre****University College Hospitals**

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**Study participating centre****John Radcliffe Hospital**

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**Study participating centre****Nottingham University Hospitals NHS Trust Headquarters**

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**Study participating centre****University Hospitals Birmingham NHS Foundation Trust**

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**Study participating centre**  
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**Study participating centre**  
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## **Sponsor information**

**Organisation**  
University of Birmingham

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

## **Funder(s)**

**Funder type**

Charity

**Funder Name**

Cancer Research UK; Grant Codes: C42639/A27723, PLEXXIKON INC

**Alternative Name(s)**

CR\_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Other non-profit organizations

**Location**

United Kingdom

## Results and Publications

**Individual participant data (IPD) sharing plan**

The datasets generated during and/or analysed during the current study are/will be available upon request from the Trial Management Group by contacting [promise@trials.bham.ac.uk](mailto:promise@trials.bham.ac.uk), following the end of the study. Requests will be considered on an individual basis.

**IPD sharing plan summary**

Available on request

**Study outputs**

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