ISRCTN12451433 https://doi.org/10.1186/ISRCTN12451433

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

Submission date
17/11/2020

Recruitment status
No longer recruiting

Registration date
17/11/2020

Overall study status
Completed

Last Edited
06/01/2026

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] 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

Contact information

Type(s)
Scientific

Contact name
Prof Adam Mead

Contact details

Weatherall Institute for Molecular Medicine
John Radcliffe Hospital
Oxford
United Kingdom
OX3 9DS
+44 (0)1865 222 489
adam.mead@imm.ox.ac.uk

Type(s)
Scientific

Contact name
Mr Joseph Rogers

Contact details
Cancer Research UK Clinical Trials Unit
Institute of Cancer and Genomic Sciences
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT
+44 1213717866
j.a.rogers@bham.ac.uk

Type(s)
Scientific

Contact name
Mrs Louise Hopkins

Contact details
Cancer Research UK Clinical Trials Unit
Institute of Cancer and Genomic Sciences
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT
+44 1213717861
l.m.hopkins@bham.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2019-000916-27

Integrated Research Application System (IRAS)
261523

Central Portfolio Management System (CPMS)
46423

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

Primary study design
Interventional

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

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 >=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 >=24 weeks of ruxolitinib with ongoing residual splenomegaly >5cm from costal margin
4. Platelets >75x109/L
5. Neutrophils >1.0x109/L
6. <10% blasts in peripheral blood and/or bone marrow
7. Coagulation (INR or PT) and Activated partial thromboplastin time <=1.5 x 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 <=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 <=2.0 × ULN OR Direct bilirubin <=ULN for patients with total bilirubin >2.0 × ULN
13.1. Exception for elevated total bilirubin secondary to Gilbert’s disease, in which case it must be <=3 x ULN
14. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <=2.0 × 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 >=1 year
5. Ongoing systemic infection requiring treatment with antibiotic, antiviral, or antifungal treatment
6. ECOG Performance Status Score >= 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) > = 450 msec males or QTcF > = 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 <=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 µg (NIH 2020) (Note: Patients who switch from a high dose to a dose of 30 µg/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
England
NE7 7DN

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
England
LE1 5WW

Study participating centre
University College Hospitals
250 Euston Road
1st Floor Central
London
England
NW1 2PG

Study participating centre
John Radcliffe Hopsital
Headley Way
Oxford
England
OX3 9DU

Study participating centre
Nottingham University Hospitals NHS Trust Headquarters
QMC Campus
Derby Road
Nottingham
England
NG7 2UH

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way
Edgbaston

Birmingham
England
B15 2GW

Study participating centre
Northern General Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Herries Road
Sheffield
England
S5 7AU

Study participating centre
St James University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
Leeds
England
LS9 7TF

Study participating centre
Guy's Hospital
16th Floor, Tower Wing
Great Maze Pond
London
England
SE1 9RT

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, 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?
HRA research summary			28/06/2023	No	No