

# Ruxolitinib versus hydroxycarbamide or interferon as first-line therapy in high-risk polcythemia vera

<b>Submission date</b> 20/08/2019	<b>Recruitment status</b> Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 28/08/2019	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 06/06/2025	<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-comparing-ruxolitinib-with-best-available-treatment-for-polycythaemia-vera-mithridate>

## Contact information

### Type(s)

Scientific

### Contact name

Prof Claire Harrison

### Contact details

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## Additional identifiers

### EudraCT/CTIS number

2018-001908-11

### IRAS number

### ClinicalTrials.gov number

NCT04116502

## Secondary identifying numbers

RG\_16-148; CPMS: 39201

# Study information

## Scientific Title

A phase III, randomised, open-label, Multicenter International Trial comparing ruxolitinib with either HydRoxycarbamiDe or interferon Alpha as first-line ThErapy for high-risk polycythemia vera (MITHRIDATE)

## Acronym

MITHRIDATE

## Study objectives

To compare the time to the combined incidence of; major thrombosis, major haemorrhage, death or transformation to MDS, AML or post-PV (PPV) MF in high-risk PV patients randomised to ruxolitinib versus standard care.

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Approved 16/08/2019, London-Fulham Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; Tel: +44 (0)207 104 8235; Email: nrescommittee.london-fulham@nhs.net), REC ref: 19/LO/0951

## Study design

Phase III randomised-controlled multi-centre international open-label trial

## Primary study design

Interventional

## Secondary study design

Randomised controlled trial

## Study setting(s)

Hospital

## Study type(s)

Treatment, Efficacy

## Participant information sheet

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

Polycythaemia vera

## Interventions

The interventions are Arm A: Ruxolitinib and Arm B: Best Available Therapy (Hydroxycarbamide OR Interferon Alpha, any formulation permitted), which will be selected by the Investigator prior to randomisation. Randomisation will be in a 1:1 ratio and will be performed using a bespoke

computer randomisation system developed by the Cancer Research UK Clinical Trials Unit (CRCTU) employing a stratified minimisation method.

Patients will be stratified by:

1. Country of Origin: UK, France
2. Elected standard of care therapy: IFN, HC
3. Age: <60, ≥ 60
4. Prior thrombosis: No, Yes
5. Length of time from diagnosis: <5, ≥5 years
6. Cardiovascular risk factors, (including the following: arterial hypertension, diabetes, dyslipidemia, tobacco use, obesity): No, Yes

Randomisation will be in a 1:1 ratio AND There will be no cross-over either between arm A and B or between therapies on Arm B.

Arm A: Ruxolitinib – starting dose of 10 mg adjusted in line with the summary product of characteristics throughout for treatment period of 3 years

Arm B: Best Available Therapy (Hydroxycarbamide OR interferon alpha (any formulation permitted)) – treatment for 3 years, dosage is in line with the summary product of characteristics

Patients will be required to attend for study visits to monitor their disease, as they would do whilst following standard care. In addition, patients will be asked to consent to complete quality of life questionnaires every few months and have an additional bone marrow biopsy and an ultrasound scan at 3 years.

### **Intervention Type**

Drug

### **Pharmaceutical study type(s)**

Not Applicable

### **Phase**

Phase III

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

Ruxolitinib, hydroxycarbamide, interferon alpha (any formulation permitted)

### **Primary outcome measure**

Event Free Survival (EFS): defined as the time from randomisation to the date of the first event including;

1. Major thrombosis
2. Major haemorrhage
3. Death
4. Transformation to MDS, AML or PPV-MF

Patients who do not experience an event during the trial will be censored at their date last seen

### **Secondary outcome measures**

1. Major thrombosis (both combined and split into venous and arterial)
2. Major haemorrhage
3. Transformation to PPV-MF
4. Transformation to AML and/or MDS
5. Complete haematological response (CHR) as defined by ELN response criteria at 1 year

6. Symptom burden/(QALY) quality of life years gained
7. Health economics including cost-utility and cost-effectiveness analyses
8. Peripheral blood JAK2 V617F allele burden according to ELN response criteria
9. Rates of discontinuation
10. Adverse events
11. Spleen response in patients with splenomegaly at baseline
12. Time free from venesection
13. Rate of second malignancies
14. Change in QRisk score

**Overall study start date**

16/08/2019

**Completion date**

30/09/2029

## Eligibility

**Key inclusion criteria**

Current participant inclusion criteria as of 06/06/2025:

1. Patient  $\geq 18$  years of age
  2. Diagnosis of PV meeting WHO criteria within the past 15 years
  3. Meets criteria of high-risk PV, defined as  $WBC > 11 \times 10^9/l^*$  AND at least ONE of the following:
    - 3.1. Aged  $> 60$  years
    - 3.2. Prior thrombosis or major haemorrhage related to disease
    - 3.3. Platelet count  $> 1000 \times 10^9/l^*$
    - 3.4. Hypertension or diabetes requiring pharmacological therapy
  - \* at any time after diagnosis
  4. Patients must have a screening haemoglobin of  $> 8g/dl$
  5. Patients may have received antiplatelet agents and venesection
  6. Patients may have received ONE or less cytoreductive therapy for less than 10 years (BUT they should not be resistant or intolerant to that therapy)
  7. Able to provide written informed consent
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Previous participant inclusion criteria as of 09/05/2023:

1. Patient 18 years of age or over
  2. Diagnosis of PV meeting WHO criteria within the past 10 years
  3. Meets criteria of high-risk PV, defined as  $WBC > 11 \times 10^9/l$  AND at least ONE of the following:
    - 3.1. Aged  $> 60$  years
    - 3.2. Prior thrombosis or major haemorrhage related to disease
    - 3.3. Platelet count  $> 1000 \times 10^9/l$  at any time after diagnosis
    - 3.4. Diagnosed  $< 10$  years
    - 3.5. Received treatment for  $< 5$  years
  4. Patients may have received antiplatelet agents and venesection
  5. Patients may have received ONE or less cytoreductive therapy for less than 5 years (BUT they should not be resistant or intolerant to that therapy)
  6. Able to provide written informed consent
-

Previous participant inclusion criteria:

1. Patient 18 years of age or over
2. Diagnosis of PV meeting WHO criteria within the past 10 years
3. Meets criteria of high risk\* PV, defined as WBC > 11 x 10<sup>9</sup>/l\* AND at least ONE of the following:
  - 3.1. Age > 60 years
  - 3.2. Prior thrombosis or major haemorrhage related to disease
  - 3.3. Platelet count > 1000 x 10<sup>9</sup>/l\*
  - 3.4. Diagnosed < 10 years
  - 3.5. Received treatment for < 5 years)
4. Patients may have received antiplatelet agents and venesection
5. Patients may have received ONE or less cytoreductive therapy for less than 5 years (BUT they should not be resistant or intolerant to that therapy)
6. Able to provide written informed consent

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

Patient

### **Age group**

Adult

### **Lower age limit**

18 Years

### **Sex**

Both

### **Target number of participants**

Planned Sample Size: 586; UK Sample Size: 293

### **Key exclusion criteria**

Current participant exclusion criteria as of 06/06/2025:

1. Diagnosis of PV > 15 years previously
2. Absence of JAK-2 mutation
3. Patients with any contraindications to any of the investigational medical products
4. Treatment with >1 cytoreductive therapy OR a cytoreductive treatment duration exceeding 10 years OR resistance/intolerance to that therapy
5. Active infection including Human Immunodeficiency Virus (HIV), hepatitis B, hepatitis C, autoimmune hepatitis, tuberculosis
6. Pregnant or lactating patients (Women of childbearing potential must have a negative urine or blood Human Chorionic Gonadotropin pregnancy test prior to trial entry)
7. Patients with lactose allergies, hypersensitivities, or rare hereditary problems, of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
8. Patients with uncontrolled neuropsychiatric disorders
9. Patients with uncontrolled cutaneous cancers
10. Patients and partners not prepared to adopt highly effective contraception measures (if sexually active) whilst on treatment and for at least 6 months after completion of study medication
11. ECOG Performance Status Score  $\geq 3$

12. Uncontrolled rapid or paroxysmal atrial fibrillation, uncontrolled or unstable angina, recent (within the last 6 months) myocardial infarction or acute coronary syndrome or any clinically significant cardiac disease > NYHA ( New York Heart Association) Class II
13. Patients who have transformed to myelofibrosis
14. Previous treatment with ruxolitinib
15. Previous (within the last 12 months) or current platelet count <100 x 10<sup>9</sup>/L or neutrophil count < 1 x 10<sup>9</sup>/L not due to therapy
16. Inadequate liver function as defined by ALT/AST >2.0 x ULN
17. Inadequate renal function as defined by eGFR < 30 mls/min
18. Unable to give informed consent

**Additional Exclusion Criteria for France Only:**

19. All women of childbearing potential (as per Appendix 8 definition)
  20. No affiliation with the French healthcare system
  21. Persons under psychiatric care who would impede understanding of informed consent and optimal treatment and follow-up
  22. Adults subject to a legal protection measure (guardianship, curatorship and safeguard of justice)
  23. Patients deprived of their liberty by a judicial or administrative decision
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**Previous participant inclusion criteria:**

1. Diagnosis of PV >10 years previously
2. Absence of JAK-2 mutation
3. Patients with any contraindications to any of the investigational medical products
4. Treatment with >1 cytoreductive therapy OR a cytoreductive treatment duration exceeding 5 years OR resistance/intolerance to that therapy
5. Active infection including hepatitis B, hepatitis C, Tuberculosis
6. Pregnant or lactating patients (Women of childbearing potential must have a negative urine or blood Human Chorionic Gonadotropin pregnancy test prior to trial entry)
7. Patients and partners of childbearing potential not prepared to adopt highly effective contraception measures (if sexually active) whilst on treatment and for at least 6 months after completion of study medication
8. ECOG Performance Status Score ≥3
9. Uncontrolled rapid or paroxysmal atrial fibrillation, uncontrolled or unstable angina, recent (within the last 6 months) myocardial infarction or acute coronary syndrome or any clinically significant cardiac disease > NYHA (New York Heart Association) Class II
10. Patients who have transformed to myelofibrosis
11. Previous treatment with ruxolitinib
12. Previous (within the last 12 months) or current platelet count <100 x 10<sup>9</sup>/L or neutrophil count < 1 x 10<sup>9</sup>/L not due to therapy
13. Inadequate liver function as defined by ALT/AST >2.0 x ULN
14. Inadequate renal function as defined by eGFR < 30 ml/min
15. Unable to give informed consent

**Date of first enrolment**

30/09/2019

**Date of final enrolment**

30/10/2025

# Locations

## Countries of recruitment

England

France

Northern Ireland

Scotland

United Kingdom

Wales

## Study participating centre

### Guys Hospital

Guys Hospital

Great Maze Pond

London

United Kingdom

SE1 9RT

## Study participating centre

### Churchill Hospital

Churchill Hospital

Old Road

Headington

Oxford

United Kingdom

OX3 7LE

## Study participating centre

### Nottingham City Hospital

Hucknall Road

Nottingham

United Kingdom

NG5 1PB

## Study participating centre

### Addenbrookes

Addenbrookes Hospital

Hills Road

Cambridge  
United Kingdom  
CB2 0QQ

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

**Study participating centre**  
**Kent and Canturbury Hospital**  
Ethelbert Road  
Canterbury  
United Kingdom  
CT1 3NG

**Study participating centre**  
**Worthing Hospital**  
Lyndhurst Road  
Worthing  
United Kingdom  
BN11 2DH

**Study participating centre**  
**St Richard's Hospital**  
Spitalfield Lane  
Chichester  
United Kingdom  
PO19 6SE

**Study participating centre**  
**University Hospital of Wales**  
Heath Park  
Cardiff  
United Kingdom  
CF14 4XW



**Study participating centre**  
**Royal Gwent Hospital**  
Cardiff Road  
Newport  
United Kingdom  
NP20 2UB

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

**Study participating centre**  
**Royal Berkshire Hospital**  
Royal Berkshire Hospital  
London Road  
Reading  
United Kingdom  
RG1 5AN

**Study participating centre**  
**Sunderland Royal Hospital**  
Kayll Road  
Sunderland  
United Kingdom  
SR4 7TP

**Study participating centre**  
**Aberdeen Royal Infirmary**  
Foresterhill Road  
Aberdeen  
United Kingdom  
AB25 2ZN

**Study participating centre**  
**Gloucestershire Royal Hospital**  
Great Western Road  
Gloucester

United Kingdom  
GL1 3NN

**Study participating centre**  
**Colchester General Hospital**  
Colchester District General Hosp.  
Charter Way  
Turner Road  
Colchester  
United Kingdom  
CO4 5JL

**Study participating centre**  
**Huddersfield Royal Infirmary**  
Acre Street  
Huddersfield  
United Kingdom  
HD3 3EA

**Study participating centre**  
**Calderdale Royal Hospital Pts Control**  
The Calderdale Royal Hospital  
Godfrey Road  
Salterhebble  
Halifax  
United Kingdom  
HX3 0PW

**Study participating centre**  
**Castle Hill Hospital**  
Entrance 3  
Castle Road  
Cottingham  
United Kingdom  
HU16 5JQ

**Study participating centre**  
**Warwick Hospital**  
Lakin Road

Warwick  
United Kingdom  
CV34 5BW

**Study participating centre**  
**Western General Hospital**  
Crewe Road South  
Edinburgh  
Lothian  
United Kingdom  
EH4 2XU

**Study participating centre**  
**St John's Hospital**  
Howden West  
Livingston  
Lothian  
United Kingdom  
EH54 6PP

**Study participating centre**  
**Raigmore Hospital**  
Old Perth Rd  
Inverness  
United Kingdom  
IV2 3UJ

**Study participating centre**  
**University College Hospital Elizabeth Garrett Anderson Wing**  
235 Euston Road  
London  
United Kingdom  
NW1 2BU

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

**Study participating centre**  
**Leicester Royal Infirmary**  
Infirmary Square  
Leicester  
United Kingdom  
LE1 5WW

**Study participating centre**  
**Arrow Park Hospital**  
Arrowe Park Hospital  
Arrowe Park Road  
Wirral  
United Kingdom  
CH49 5PE

**Study participating centre**  
**St George's Hospital**  
Blackshaw Road  
Tooting  
London  
United Kingdom  
SW17 0QT

**Study participating centre**  
**Birmingham Heartlands Hospital**  
Bordesley Green East  
Bordesley Green  
Birmingham  
United Kingdom  
B9 5SS

**Study participating centre**  
**Good Hope Hospital**  
Rectory Road  
Sutton Coldfield  
United Kingdom  
B75 7RR

**Study participating centre**

**Freeman Road Hospital**

Freeman Road  
High Heaton  
Newcastle upon Tyne  
United Kingdom  
NE7 7DN

**Study participating centre****Royal Cornwall Hospital (treiske)**

Treliske  
Truro  
United Kingdom  
TR1 3LJ

**Study participating centre****Blackpool Victoria Hospital**

Whinney Heys Road  
Blackpool  
United Kingdom  
FY3 8NR

**Study participating centre****Southampton**

Southampton General Hospital  
Tremona Road  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre****Northampton**

Northampton General Hospital  
Cliftonville  
Northampton  
United Kingdom  
NN1 5BD

**Study participating centre****Wexham Park Hospital**

Wexham Street  
Wexham

Slough  
United Kingdom  
SL2 4HL

**Study participating centre**

**Royal United Hospital**

Combe Park  
Bath  
United Kingdom  
BA1 3NG

**Study participating centre**

**Norfolk and Norwich University Hospital**

Colney Lane  
Colney  
Norwich  
United Kingdom  
NR4 7UY

**Study participating centre**

**The James Cook University Hospital**

Marton Road  
Middlesbrough  
United Kingdom  
TS4 3BW

**Study participating centre**

**Northumbria Healthcare NHS Foundation Trust**

North Tyneside General Hospital  
Rake Lane  
North Shields  
United Kingdom  
NE29 8NH

**Study participating centre**

**Southmead Hospital**

Southmead Road  
Westbury-on-trym  
Bristol  
United Kingdom  
BS10 5NB

**Study participating centre**  
**Belfast City Hospital**  
51 Lisburn Rd  
Belfast  
United Kingdom  
BT9 7AB

**Study participating centre**  
**Kettering General Hospital**  
Rothwell Road  
Kettering  
United Kingdom  
NN16 8UZ

**Study participating centre**  
**Halton General Hospital**  
Hospital Way  
Halton  
Runcorn  
United Kingdom  
WA7 2DA

**Study participating centre**  
**New Cross Hospital**  
Wolverhampton Road  
Wolverhampton  
United Kingdom  
WV10 0QP

**Study participating centre**  
**Russells Hall Hospital**  
Pensnett Road  
Dudley  
United Kingdom  
DY1 2HQ

**Study participating centre**

**Wythenshawe Hospital**

Southmoor Road  
Wythenshawe  
Manchester  
United Kingdom  
M23 9LT

**Study participating centre****Derriford Hospital**

Derriford Road  
Crownhill  
Plymouth  
United Kingdom  
PL6 8DH

**Study participating centre****Royal Hallamshire Hospital**

Glossop Road  
Sheffield  
United Kingdom  
S10 2JF

**Study participating centre****York Hospital**

Wigginton Road  
York  
United Kingdom  
YO31 8HE

**Sponsor information****Organisation**

University of Birmingham

**Sponsor details**

Edgbaston  
Birmingham  
England  
United Kingdom



B15 2TT  
+44 (0)121 414 3792  
mithridate@trials.bham.ac.uk

**Sponsor type**

University/education

**Website**

<http://www.birmingham.ac.uk/>

**ROR**

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

## **Funder(s)**

**Funder type**

Industry

**Funder Name**

Novartis

**Alternative Name(s)**

Novartis AG, Novartis International AG

**Funding Body Type**

Government organisation

**Funding Body Subtype**

For-profit companies (industry)

**Location**

Switzerland

**Funder Name**

MPN Voice

## **Results and Publications**

**Publication and dissemination plan**

There will be a trial website (currently under construction so URL unavailable ) that will include the protocol, patient documents etc. for sites to download.

Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham.

Intellectual property rights will be addressed in the corresponding contracts between Sponsor and national coordinating centres/sites.

Individual countries will be allowed to publish their efficacy results, however, the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the TMG decides otherwise.

### **Intention to publish date**

30/09/2029

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

The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Claire Harrison (Claire.Harrison@gstt.nhs.uk).

### **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>			26/07/2023	No	No