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

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| **Submission date**<br>20/08/2019 | **Recruitment status**<br>Recruiting | [X] Prospectively registered<br>[_] Protocol<br>[_] Statistical analysis plan<br>[_] Results<br>[_] Individual participant data<br>[X] Record updated in last year |
| **Registration date**<br>28/08/2019 | **Overall study status**<br>Ongoing | |
| **Last Edited**<br>21/10/2026 | **Condition category**<br>Cancer | |

**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**
Guys and St Thomas NHS Foundation Trust
London
United Kingdom
SE1 9RT
+44 (0)207 188 2742
Claire.Harrison@gstt.nhs.uk

## Additional identifiers

**ClinicalTrials.gov (NCT)**
NCT04116502

**Clinical Trials Information System (CTIS)**
2018-001908-11

**Protocol serial number**
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

### Primary study design
Interventional

### Study design
Phase III randomised-controlled multi-centre international open-label trial

### Study type(s)
Efficacy, Treatment

### 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

### Phase
Phase III

### Drug/device/biological/vaccine name(s)
Ruxolitinib, hydroxycarbamide, interferon alpha (any formulation permitted)

### Primary outcome(s)
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

### Key secondary outcome(s)
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

### Completion date
30/09/2029

## Eligibility

## Key inclusion criteria

Current participant inclusion criteria as of 06/06/2025:
1. Patient ≥ 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 x 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 x 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 x 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 x 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

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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 109/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 109/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

## Healthy volunteers allowed
No

## Age group
Mixed

## Lower age limit
18 Years

## Upper age limit
100 Years

## Sex
All

## Total final enrolment
0

## 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 ≥ 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 109/L or neutrophil count < 1 x 109/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 109/L or neutrophil count < 1 x 10(9)/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
31/01/2027

## Locations

### Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

France

**Study participating centre**
**Guys Hospital**
Guys Hospital
Great Maze Pond
London
England
SE1 9RT

**Study participating centre**
**Churchill Hospital**
Churchill Hospital
Old Road
Headington
Oxford
England
OX3 7LE

**Study participating centre**
**Nottingham City Hospital**
Hucknall Road
Nottingham
England
NG5 1PB

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

**Study participating centre**
**Royal Bournemouth General Hospital**
Castle Lane East

Bournemouth
England
BH7 7DW

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

**Study participating centre**
**Worthing Hospital**
Lyndhurst Road
Worthing
England
BN11 2DH

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

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

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

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

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

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

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

**Study participating centre**
**Gloucestershire Royal Hospital**
Great Western Road
Gloucester
England
GL1 3NN

**Study participating centre**
**Colchester General Hospital**
Colchester District General Hosp.
Charter Way

Turner Road
Colchester
England
CO4 5JL

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

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

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

**Study participating centre**
**Warwick Hospital**
Lakin Road
Warwick
England
CV34 5BW

**Study participating centre**
**Western General Hospital**
Crewe Road South
Edinburgh
Lothian

Scotland
EH4 2XU

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

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

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

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

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

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

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

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

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

**Study participating centre**
**Freeman Road Hospital**
Freeman Road
High Heaton
Newcastle upon Tyne
England
NE7 7DN

**Study participating centre**

**Royal Cornwall Hospital (treliske)**
Treliske
Truro
England
TR1 3LJ

**Study participating centre**
**Blackpool Victoria Hospital**
Whinney Heys Road
Blackpool
England
FY3 8NR

**Study participating centre**
**Southampton**
Southampton General Hospital
Tremona Road
Southampton
England
SO16 6YD

**Study participating centre**
**Northampton**
Northampton General Hospital
Cliftonville
Northampton
England
NN1 5BD

**Study participating centre**
**Wexham Park Hospital**
Wexham Street
Wexham
Slough
England
SL2 4HL

**Study participating centre**
**Royal United Hospital**
Combe Park
Bath

England
BA1 3NG

**Study participating centre**
**Norfolk and Norwich University Hospital**
Colney Lane
Colney
Norwich
England
NR4 7UY

**Study participating centre**
**The James Cook University Hospital**
Marton Road
Middlesbrough
England
TS4 3BW

**Study participating centre**
**Northumbria Healthcare NHS Foundation Trust**
North Tyneside General Hospital
Rake Lane
North Shields
England
NE29 8NH

**Study participating centre**
**Southmead Hospital**
Southmead Road
Westbury-on-trym
Bristol
England
BS10 5NB

**Study participating centre**
**Belfast City Hospital**
51 Lisburn Rd
Belfast
Northern Ireland
BT9 7AB

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

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

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

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

**Study participating centre**
**Wythenshawe Hospital**
Southmoor Road
Wythenshawe
Manchester
England
M23 9LT

**Study participating centre**

**Derriford Hospital**
Derriford Road
Crownhill
Plymouth
England
PL6 8DH

**Study participating centre**
**Royal Hallamshire Hospital**
Glossop Road
Sheffield
England
S10 2JF

**Study participating centre**
**York Hospital**
Wigginton Road
York
England
YO31 8HE

**Study participating centre**
**George Eliot Hospital**
Lewis House
College Street
Nuneaton
England
CV10 7DJ

**Study participating centre**
**University Hospital (coventry)**
Clifford Bridge Road
Coventry
England
CV2 2DX

**Study participating centre**
**Ipswich Hospital**
Heath Road

Ipswich
England
IP4 5PD

**Study participating centre**
**Glan Clwd Hospital**
Ysbyty Glan Clwydd
Bodelwyddan
Rhyl
England
LL18 5UJ

# Sponsor information

**Organisation**
University of Birmingham

**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

## 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? |
|---|---|---|---|---|---|
| HRA research summary | | | 26/07/2023 | No | No |