

# Effects of tamoxifen in patients with myeloproliferative disorders

<b>Submission date</b> 13/06/2016	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 20/06/2016	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 29/10/2024	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-tamoxifen-for-people-with-myeloproliferative-disorders-tamarin>

## Contact information

### Type(s)

Public

### Contact name

Mrs Sonia Fox

### Contact details

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## Additional identifiers

### EudraCT/CTIS number

2015-005497-38

### IRAS number

### ClinicalTrials.gov number

### Secondary identifying numbers

30849

# Study information

## Scientific Title

Effects of TAMoxifen on the Mutant Allele Burden and Disease Course in Patients with Myeloproliferative Neoplasms

## Acronym

TAMARIN

## Study objectives

The aim of this study is to assess whether giving tamoxifen to patients receiving therapy for their MPN reduces the number of mutated cells found in the blood by  $\geq 50\%$  after 24 weeks of treatment compared to the start of the study.

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

East Midlands – Derby Research Ethics Committee, 24/05/2016, ref: 16/EM/0181

## Study design

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

## Primary study design

Interventional

## Secondary study design

Non randomised study

## Study setting(s)

Hospital

## Study type(s)

Treatment

## Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

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

Myeloproliferative neoplasms

## Interventions

Patients who consent to participate in the study will need to attend hospital at baseline to receive a medical exam (including palpation of the liver and spleen), blood tests (including a full fasting lipid profile), an abdominal ultrasound if they have PV or ET and a blood sample taken for central review at Cambridge Blood and Stem Cell Biobank to ensure that they are eligible for the trial and that it is safe for them to enter the trial. Patients will also be asked to complete a short Quality of Life questionnaire which has been developed specifically for patients with MPNs.

Once registered to the study, patients will have a minimum of 24 weeks of treatment with tamoxifen at 20mg od as an oral tablet.

Patients will be seen 2 weeks after starting treatment for blood tests and a medical exam and then again at weeks 4, 8, 12, 18 and 24. At weeks 12 and 24 they will also have a blood sample taken for central review at Cambridge and a full fasting lipid profile. At week 24, the patient will also be asked to have a bone marrow aspirate and trephine biopsy and complete the same Quality of Life Questionnaire they completed at baseline. If the patient had an enlarged spleen on the baseline ultrasound, an ultrasound may be repeated at any point during the 24 weeks if the blood counts suggest the patient is in Complete Response.

If the patient continues trial therapy beyond 24 weeks, they will be seen a minimum of 12 weekly for blood tests and a medical exam.

Patients will also be required to attend their local hospital 28 days after the final dose of tamoxifen for blood tests and a medical exam.

### **Intervention Type**

Drug

### **Phase**

Not Applicable

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

Tamoxifen

### **Primary outcome measure**

Primary outcome measures as of 19/11/2018:

Reduction in the peripheral blood JAK2V617F, CALR 5bp insertion (exon 9) or CALR 52bp deletion (exon 9) mutant allele burden of  $\geq 50\%$  at 24 weeks measured using validated assays for JAK2 and CALR.

Primary outcomes as of 27/06/2017:

Reduction in the peripheral blood JAK2V617F, CALR 5bp insertion (exon 9) or CALR 52bp deletion (exon 9) mutant allele burden of  $\geq 50\%$  is measured using validated assays for JAK2 and CALR respectively at baseline and 24 weeks.

Previous primary outcomes:

Peripheral blood JAK2V617F or CALR mutant allele burden is measured using validated assays for JAK2V617F and CALR respectively at baseline and 24 weeks.

### **Secondary outcome measures**

Secondary outcome measures as of 19/11/2018:

1. Proportion of patients with a reduction in the peripheral blood JAK2-V617F, CALR 5bp insertion (exon 9), or CALR 52bp deletion (exon 9) mutant allele burden of  $\geq 50\%$  at 12 weeks
2. Toxicity measured as the number of grade 3 and 4 adverse events reported.
3. The number of thrombotic events of any grade reported and validated.
4. Duration of haematological response calculated as time from registration to progression for patients who enter the study in response (CR or PR). For patients who enter the trial in stable disease, the time between first recorded response to the date of progression. Progression is defined as loss of response for PV/ET patients and evidence of disease progression for MF patients. PV/ET patients who continue to achieve a response, or MF patients who have no evidence of disease progression at the end of the trial will be censored at date last seen.

Haematological response is defined according to 2009 ELN criteria for ET/PV patients [1] and no evidence of disease progression for MF patients according to IWG-MRT response criteria [2] (for criteria see Appendices 5 & 6)

5. Proportion of patients in each response category according to IWG-MRT response criteria [2] for MF patients and 2013 ELN response criteria [3] for ET/PV patients at 24 weeks of treatment

6. Proportion of patients showing an improvement in response category at 24 weeks compared to baseline according to 2009 ELN criteria for ET/PV patients [1] and according to IWG-MRT response criteria [2] for MF patients. Patients who are in a higher category at week 24 compared to baseline will be classed a success. Patients who enter the trial in CR and who maintain a CR will also be classed as a success in this outcome

#### Exploratory Outcome Measures:

1. Change in allele burden between weeks 12, 24 and baseline.
2. Proportion of patients showing a decrease in requirement for cytoreduction at 24 weeks compared to baseline
3. Proportion of patients showing a decrease in allele burden of  $\geq 50\%$  at 36 and 48 weeks compared to baseline
4. Duration of reduction in the mutant allele burden, defined as time from first observed reduction of  $\geq 50\%$  until reduction from baseline becomes  $< 25\%$  or patients death.
5. Expression (RNAseq), DNA-protein interaction (ChIPseq) and methylation studies focused on oestrogen receptor signalling in haematopoietic progenitors obtained from peripheral blood and bone marrow before (peripheral blood only) and after tamoxifen treatment

#### Secondary outcome measures as of 27/06/2017:

1. Proportion of patients with a reduction in the peripheral blood JAK2-V617F, CALR 5bp insertion (exon 9), or CALR 52bp deletion (exon 9) mutant allele burden of  $\geq 50\%$  is measured using validated assays for JAK2 and CALR respectively at baseline and 12 weeks
2. Toxicity measured as the number of grade 3 and 4 adverse events reported according to CTCAE for the duration of treatment and including 4 weeks after the last administration of trial treatment.
3. The number of thrombotic events of any grade reported and validated, according to CTCAE for the duration of treatment and including 4 weeks after the last administration of trial treatment
4. Duration of haematological response will be assessed by the local investigator at baseline and after two, four, eight, 12, 18 and 24 weeks of treatment according to 2009 ELN criteria for ET/PV patients and to IWG-MRT response criteria for MF patients
5. Proportion of patients in each response category according to IWG-MRT response criteria for MF patients and 2013 ELN response criteria for ET/PV patients is assessed by the local investigator after 24 weeks of treatment
6. Proportion of patients showing an improvement in response category at 24 weeks compared to baseline according to 2009 ELN criteria for ET/PV patients and according to IWG-MRT response criteria for MF patients is assessed by the local investigator after 24 weeks of treatment compared to baseline

#### Exploratory outcome measures:

1. Proportion of patients showing a decrease in JAK2-V617F, CALR 5bp insertion (exon 9), or CALR 52bp deletion (exon 9) allele burden is measured using validated assays for JAK2 and CALR respectively at baseline and 12 weeks
2. Proportion of patients showing a decrease in JAK2-V617F, CALR 5bp insertion (exon 9), or CALR 52bp deletion (exon 9) allele burden is measured using validated assays for JAK2 and CALR respectively at baseline and 24 weeks
3. Proportion of patients showing a decrease in requirement for cytoreduction as reported by

the local investigator at baseline and 24 weeks

4. The expression (RNAseq), DNA-protein interaction (CHIP-Seq) and methylation studies focused on oestrogen receptor signalling in haematopoietic progenitors will be performed in the lab of Dr Mendez-Ferrer at the University of Cambridge following the collection of peripheral blood (baseline and 24 weeks) and bone marrow aspirate samples (24 weeks only)

Previous secondary outcome measures:

1. Peripheral blood JAK2V617F or CALR mutant allele burden is measured using validated assays for JAK2V617F and CALR respectively at baseline and 12 weeks
2. Peripheral blood JAK2V617F or CALR mutant allele burden is measured using validated assays for JAK2V617F and CALR respectively at baseline and 24 weeks
3. Peripheral blood JAK2V617F or CALR mutant allele burden is measured using validated assays for JAK2V617F and CALR respectively at baseline and 12 weeks
4. Toxicity measured as the number of grade 3 and 4 adverse events reported according to CTCAE for the duration of treatment (and including 4 weeks after the last administration of trial treatment).
5. Thrombotic events of any grade reported according to CTCAE for the duration of treatment (and including 4 weeks after the last administration of trial treatment)
6. Duration of haematological response calculated as time from registration to loss of response for PV/ET patients or evidence of disease progression for MF patients. PV/ET patients who continue to achieve a response, or MF patients who have no evidence of disease progression at the end of the trial will be censored at date last seen
7. Response according to IWG-MRT response criteria for MF and 2013 ELN response for ET/PV measured at 24 weeks

**Overall study start date**

25/11/2015

**Completion date**

17/02/2021

## Eligibility

### Key inclusion criteria

Current inclusion criteria as of 27/06/2017:

1. Age  $\geq 60$  years (men aged between 50-59 may also be considered following discussion with the Chief Investigator)
2. Women must be post-menopausal (defined as amenorrhoeic for at least 12 consecutive months following cessation of all exogenous hormonal treatments)
3. Confirmed diagnosis of JAK2-V617F, CALR 5bp insertion (exon 9) or CALR 52bp deletion (exon 9) positive Essential Thrombocythaemia (ET), Polycythaemia Vera (PV) or Myelofibrosis (MF) (primary or secondary) for  $\geq 6$  months
4. JAK2-V617F, CALR 5bp insertion (exon 9) or CALR 52bp deletion (exon 9) mutant allele burden  $\geq 20\%$  in peripheral blood granulocyte DNA at study entry (assessed via central review)
5. WHO performance status 0-2
6. For patients with PV or ET, maintenance of platelet count  $\leq 600 \times 10^9/L$ , WBC  $\leq 25 \times 10^9/L$  and venesection requirements  $\leq 1$  per month for the previous 3 months prior to registration, without introduction of any new therapeutic agents for their MPN for 6 months prior to registration
7. For patients with MF, there must not have been any evidence of disease progression\* for the previous 6 months (prior to registration) and no new therapeutic agents for their MPN introduced during this period

8. Patients receiving cytoreductive therapy (with the exception of interferon alpha or investigational agents) for their MPN (not solely aspirin or venesection)
9. Adequate hepatic function, defined as:
  - 9.1. bilirubin  $\leq 1.5 \times$  ULN (patients with elevated bilirubin due to Gilbert's syndrome are eligible)
  - 9.2. AST/ALT/ALP  $\leq 2.5 \times$  ULN
10. Adequate renal function (creatinine clearance  $>30$  mL/min)
11. Male patients must agree to use effective contraception during participation in the trial and for 2 months after the last dose of trial treatment
12. Patient must be able to give written informed consent

\*Defined by IWG-MRT ELN criteria. Please note no baseline bone marrow is required to confirm absence of "Leukemic transformation confirmed by a bone marrow blast count of  $\geq 20\%$ ".

Previous inclusion criteria:

1. Age  $\geq 60$  years (men aged between 50-59 may also be considered following discussion with the Chief Investigator)
2. Women must be post-menopausal (defined as amenorrhoeic for at least 12 consecutive months following cessation of all exogenous hormonal treatments)
3. Confirmed diagnosis of JAK2-V617F or CALR positive Essential Thrombocythaemia (ET), Polycythaemia Vera (PV) or Myelofibrosis (MF) (primary or secondary) for  $\geq 6$  months
4. JAK2-V617F or CALR mutant allele burden  $\geq 20\%$  in peripheral blood granulocyte DNA at study entry (assessed via central review)
5. WHO performance status 0-2
6. For patients with PV or ET, maintenance of at least a partial haematological response according to 2009 ELN criteria must have been achieved for the previous 6 months (prior to registration), without introduction of any new therapeutic agents for their MPN
7. For patients with MF, there must not have been any evidence of disease progression\* for the previous 6 months (prior to registration) and no new therapeutic agents for their MPN introduced during this period.
8. Patients receiving cytoreductive therapy for their MPN (not solely aspirin or venesection)
9. Adequate hepatic function, defined as:
  - 9.1. bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN) (patients with elevated bilirubin due to Gilbert's syndrome are eligible)
  - 9.2. AST/ALT/ALP  $\leq 2.5 \times$  ULN
10. Adequate renal function (creatinine clearance  $> 30$  mL/min)
11. Male patients must agree to use effective contraception during participation in the trial and for 2 months after the last dose of trial treatment
12. Patient must be able to give written informed consent

\*Defined by IWG-MRT ELN criteria (Appendix 6). Please note no baseline bone marrow is required to confirm absence of "Leukemic transformation confirmed by a bone marrow blast count of  $\geq 20\%$ "

## **Participant type(s)**

Patient

## **Age group**

Adult

## **Sex**

Both

## Target number of participants

Planned Sample Size: 42; UK Sample Size: 42

## Total final enrolment

38

## Key exclusion criteria

Current exclusion criteria as of 27/06/2017:

1. Leukaemic transformation (>20% blasts in blood, marrow or extramedullary site).
2. Accelerated phase of disease as indicated by  $\geq 10\%$  blasts in the peripheral blood
3. Treatment of ET, PV or MF with Interferon alpha or other investigational agents for their MPN within 6 months prior to trial entry. JAK inhibitors, such as ruxolitinib, are allowed if taken continuously for  $\geq 6$  months prior to registration (dose changes during that period will be allowed)
4. Any of the following previous thrombotic events at any time:
  - 4.1. Portal or other splanchnic venous thrombosis
  - 4.2. Vascular access complication
  - 4.3. Ischemia cerebrovascular
  - 4.4. Stroke
  - 4.5. Transient Ischaemic attack
  - 4.6. Superficial thrombophlebitis
  - 4.7. Venous Thromboembolic events including pulmonary embolism (PE) and deep vein thrombosis (DVT)
  - 4.8. Peripheral vascular ischemia
  - 4.9. Visceral arterial ischemia
  - 4.10. Acute coronary syndrome
  - 4.11. Myocardial infarction
5. Previous malignancy within 5 years with the exception of adequately treated cervical carcinoma in situ or localized non-melanoma skin cancer
6. Previous endometrial cancer, hyperplasia or polyps
7. Prior treatment with hematopoietic stem cell transplantation
8. Patients who do not carry JAK-2V617F, CALR 5bp insertion (exon 9) or CALR 52bp deletion (exon 9) mutations, or whose allele burden is  $< 20\%$  at study entry (assessed via central review)
9. Female patients receiving hormone replacement therapy
10. Hypertriglyceridemia  $>$  grade 1
11. Any serious underlying medical condition (at the judgment of the Investigator), which could impair the ability of the patient to participate in the trial (e.g. liver disease, active autoimmune disease, uncontrolled diabetes, uncontrolled infection (HIV, Hepatitis B and C), known genetic defect (apart from MPN) relating to venous thromboembolic events, or psychiatric disorder precluding understanding of trial information)
12. Known hypersensitivity to tamoxifen or hypersensitivity to any other component of tamoxifen
13. Concomitant drugs contraindicated for use with the trial drug according to the Summary of Product Characteristics (Appendix 8)
14. Known planned scheduled elective surgery during study with the exception of dental and low risk eye surgery (e.g. cataracts)

Previous exclusion criteria:

1. Leukaemic transformation ( $> 20\%$  blasts in blood, marrow or extramedullary site).
2. Accelerated phase of disease as indicated by  $> 5\%$  blasts in the peripheral blood
3. Treatment of ET, PV or MF with Interferon alpha or JAK inhibitors, such as ruxolitinib, or other

investigational agents for their MPN within 6 months prior to trial entry

4. Any of the following previous thrombotic events at any time:

4.1. Portal or other splanchnic venous thrombosis

4.2. Vascular access complication

4.3. Ischemia cerebrovascular

4.4. Stroke

4.5. Transient Ischaemic attack

4.6. Superficial thrombophlebitis

4.7. Venous Thromboembolic events including pulmonary embolism (PE) and deep vein thrombosis (DVT)

4.8. Peripheral vascular ischemia

4.9. Visceral arterial ischemia

4.10. Acute coronary syndrome

4.11. Myocardial infarction

5. Previous malignancy within 5 years with the exception of adequately treated cervical carcinoma in situ or localized non-melanoma skin cancer

6. Previous endometrial cancer, hyperplasia or polyps

7. Prior treatment with hematopoietic stem cell transplantation

8. Patients who do not carry any mutations in JAK2V617F or CALR or allele burden < 20%

9. Female patients receiving hormone replacement therapy

10. Hypertriglyceridemia > grade 1

11. Any serious underlying medical condition (at the judgment of the Investigator), which could impair the ability of the patient to participate in the trial (e.g. liver disease, active autoimmune disease, uncontrolled diabetes, uncontrolled infection (HIV, Hepatitis B and C), known genetic defect (apart from MPN) relating to venous thromboembolic events, or psychiatric disorder precluding understanding of trial information)

12. Known hypersensitivity to tamoxifen or hypersensitivity to any other component of tamoxifen

13. Concomitant drugs contraindicated for use with the trial drug according to the Summary of Product Characteristics

14. Known planned scheduled elective surgery during study with the exception of dental and low risk eye surgery (e.g. cataracts)

#### **Date of first enrolment**

01/08/2016

#### **Date of final enrolment**

20/06/2019

## **Locations**

#### **Countries of recruitment**

England

Northern Ireland

Scotland

United Kingdom

Wales



**Study participating centre**  
**Addenbrooke's Hospital**  
Hills Road  
Cambridge  
United Kingdom  
CB2 0QQ

**Study participating centre**  
**Beatson West of Scotland Cancer Centre**  
1053 Great Western Road  
Glasgow  
United Kingdom  
G12 0YN

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

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

**Study participating centre**  
**Churchill Hospital**  
Old Road  
Oxford  
United Kingdom  
OX3 7LJ

**Study participating centre**  
**Clatterbridge Cancer Centre**  
Clatterbridge Road Site  
Wirral

United Kingdom  
CH63 4JY

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

**Study participating centre**  
**Guy's Hospital**  
Great Maze Pond  
London  
United Kingdom  
SE1 9RT

**Study participating centre**  
**Hammersmith Hospital**  
Du Cane Road  
London  
United Kingdom  
W12 0HS

**Study participating centre**  
**Nottingham City Hospital**  
City Hospital Campus  
Nottingham  
United Kingdom  
NG5 1PB

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

**Study participating centre**

**Royal Hallamshire Hospital**

Glossop Road  
Sheffield  
United Kingdom  
S10 2JF

**Study participating centre**

**Royal Stoke University Hospital**

Newcastle Road  
Stoke-on-Trent  
United Kingdom  
ST4 6QG

**Study participating centre**

**Southampton General Hospital**

Tremona Road  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre**

**St James's University Hospital**

Beckett Street  
Leeds  
United Kingdom  
LS9 7TF

**Study participating centre**

**The Queen Elizabeth Hospital**

Edgbaston  
Birmingham  
United Kingdom  
B15 2TH

**Study participating centre**

**University College London Hospital**

235 Euston Road  
London  
United Kingdom  
NW1 2BU

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

## **Sponsor information**

**Organisation**  
University of Birmingham

**Sponsor details**  
Edgbaston  
Birmingham  
England  
United Kingdom  
B15 2TT

**Sponsor type**  
Hospital/treatment centre

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

## **Funder(s)**

**Funder type**  
Charity

**Funder Name**  
Bloodwise TAP

## **Results and Publications**

**Publication and dissemination plan**  
Results of this trial will be submitted for publication in a peer-reviewed journal.

**Intention to publish date**  
20/02/2022

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

The data sharing plans for the current study are unknown and will be made 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="#">Protocol file</a>	version 4.0	29/10/2018	31/01/2023	No	No
<a href="#">Abstract results</a>	Presented at ASH	05/11/2020	15/02/2023	No	No
<a href="#">Basic results</a>		15/02/2023	15/02/2023	No	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Results article</a>		25/11/2023	08/08/2024	Yes	No