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Effects of tamoxifen in patients with myeloproliferatIve disorders

Submission date 13/06/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 20/06/2016	**Overall study status** Completed	
Last Edited 29/10/2024	**Condition category** Cancer	

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

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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 ≥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 ≥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 ≥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 ≥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 ≥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 ≥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 ≥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 ≥ 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 ≥ 6 months
4. JAK2-V617F, CALR 5bp insertion (exon 9) or CALR 52bp deletion (exon 9) mutant allele burden ≥ 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 ≤600 x 109/L, WBC ≤25 x 109/L and venesection requirements ≤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 ≤ 1.5 x ULN (patients with elevated bilirubin due to Gilbert's syndrome are eligible)
9.2.AST/ALT/ALP ≤ 2.5 x 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 ≥20%".

Previous inclusion criteria:
1. Age ≥ 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 ≥ 6 months
4. JAK2-V617F or CALR mutant allele burden ≥ 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 ≤ 1.5 x upper limit of normal (ULN) (patients with elevated bilirubin due to Gilbert's syndrome are eligible)
9.2. AST/ALT/ALP ≤ 2.5 x 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 ≥ 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 ≥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 ≥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?
Protocol file	version 4.0	29/10/2018	31/01/2023	No	No
Abstract results	Presented at ASH	05/11/2020	15/02/2023	No	No
Basic results		15/02/2023	15/02/2023	No	No
HRA research summary			28/06/2023	No	No
Results article		25/11/2023	08/08/2024	Yes	No