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A study on the safety and effectiveness of fedratinib with ropeginterferon alfa-2b in patients with myelofibrosis

Submission date
23/05/2022

Recruitment status
No longer recruiting

Registration date
16/06/2022

Overall study status
Ongoing

Last Edited
20/01/2025

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Myelofibrosis (MF) is a rare bone marrow cancer that causes scarring of the bone marrow. The scar tissue builds up inside your bone marrow leaving blood cells unable to develop properly. Symptoms of MF include anaemia (low red cell levels), weakness, tiredness and often an enlarged spleen. MF can develop without having had any other conditions; this is called primary myelofibrosis. Secondary myelofibrosis is where the condition develops in people who have other bone marrow disorders, such as polycythaemia vera or essential thrombocythaemia.
More than 55 in 100 people (more than 55%) with MF have a change in a gene called JAK2. The JAK2 gene makes a protein that controls how many blood cells your body makes. JAK2 inhibitors are drugs that slow or stop the growth of cancer cells. They are also called cancer growth blockers. Although JAK2 inhibitors, such as ruxolitinib, and fedratinib, have shown promising results for some patients with MF, treatment with a JAK2 inhibitor does not usually cure the patient's disease.
Pegylated interferon is a type of immunotherapy that can be used to treat MF. Previous studies have shown that combining a JAK2 inhibitor with a pegylated interferon in patients with MF is safe to administer and may be more effective. This is thought to be because the interferon makes the stem cells that eventually develop into blood cells (haematopoietic cells) more sensitive to the JAK2 inhibitor.
The FEDORA study will use a selective JAK2 inhibitor called fedratinib, and a next generation pegylated interferon called ropeginterferon alfa-2b. Fedratinib has better activity against JAK2 than some other JAK2 inhibitors, and is given as an oral tablet. Ropeginterferon alfa-2b has been shown to be better tolerated than previous pegylated interferons and is self administered as an injection into the skin.
The aim of the FEDORA study is to gather more information about whether the combination of fedratinib and ropeginterferon alfa-2b is tolerated, and whether it provides a benefit to MF patients.

Who can participate?
Patients with primary or secondary MF that require treatment and have the JAK2 mutation

What does the study involve?
If participants chose to join the study they will be asked to give written informed consent and screening assessments will take place (including medical history, physical examination, blood test) to confirm if they are suitable for the study. Study participants will begin treatment with fedratinib on its own (pre-treatment)to ensure they can tolerate this treatment. After a month of pre-treatment, a low starting dose of ropeginterferon alfa-2b will be added to their treatment regimen. This dose of ropeginterferon alfa-2b will be increased every month if the participant is doing well on the combination and their blood counts are stable or reduced if they are suffering with side effects. Once a dose combination is reached that the participant is able to tolerate, they would remain on these doses for the duration of the study. We will collect information about the participant and their disease, how it responds to treatment and any side effects they experience for 2 years after the start of their treatment. Assessments will include physical examinations, blood tests, spleen assessments, quality of life questionnaires, thiamine testing andm6 monthly ultrasounds of spleen. Participants may continue on treatment for up to 2 years (24 monthly cycles). We will also collect bone marrow and blood samples at time-points which are in line with routine sample collection to monitor the participants disease.

What are the possible benefits and risks of participating?
Benefits - There is no guaranteed benefit to taking part in this study because we do not yet know whether this combination of treatments is better than the standard treatment. It is possible that the new treatment is not as good as the standard treatment. Equally, it is possible that the standard treatment is not as good which is why this study is being done. The careful monitoring you will receive if you take part in this study is a safeguard against this risk. The information gained from this study will help improve treatment for other people with MF in the future.
Risks - It is possible that you will experience side effects from your treatment whether you take part in this study or not. Treatment for MF affects all healthy cells within the bone marrow as well as the cancer cells. This means that you might not be able to produce normal numbers of red blood cells, and you might need blood transfusions. If you are not able to produce enough platelets in your blood, you could be at risk of bleeding, so treatment might need to be reduced or you might need a platelet transfusion. More importantly the white blood cell count can fall, meaning that you could be at high risk of serious infections. Your doctor will instruct you about the steps to be taken if you develop a high temperature. If you do develop a temperature this can quickly turn into a life-threatening infection without prompt treatment so it is important that you receive medical attention and antibiotics straight away. Both fedratinib and Ropeginterferon alfa-2b are known to lower patients' blood counts.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
February 2021 to June 2026

Who is funding the study?
Cure Leukaemia (UK)
Celgene (USA)
AOP Orphan Pharmaceuticals (Austria)

Who is the main contact?
Dr Catherine Thomas
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2021-004056-42

IRAS number
1003972

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 53036, IRAS 1003972

Study information

Scientific Title
A phase II study to evaluate the tolerability, safety and activity of fedratinib combined with ropeginterferon alfa-2b in patients with myelofibrosis

Acronym
FEDORA

Study objectives
Evaluate the tolerability, safety and activity of fedratinib combined with ropeginterferon alfa-2b in patients with myelofibrosis

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 30/03/2022, Yorkshire & The Humber - Leeds West Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 2071048083; bradfordleeds.rec@hra.nhs.uk), ref: 21/YH/0300

Study design
Interventional non randomized

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 participant information sheet. If you are a patient that is eligible to be considered for the FEDORA study, your doctor will discuss this with you and will be able to provide you with a copy of the participant information sheet for the trial.

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

Interventions
Treatment is delivered in 28-day cycles. During an initial pre-treatment stage, patients are established onto a stable dose of fedratinib. The starting dose of 400mg can be reduced in the event of toxicity. Once a patient has completed a 28-day cycle on a stable dose of fedratinib, combination therapy with ropeginterferon alfa-2b starts at cycle 1. Ropeginterferon alfa-2b is taken subcutaneously on days 1 and 15 of each cycle, starting at a 100 microgram dose. Ropeginterferon alfa-2b dose is escalated in 50 microgram increments at the start of each cycle, up to a maximum of 250 microgram, as long at the patient is tolerating combination treatment. Trial treatment will continue for up to 2 years. Patients will be followed-up monthly whilst on trial treatment, and then every 3 months following treatment completion or discontinuation, to monitor survival, progression and subsequent treatments until the end of the trial.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
fedratinib, ropeginterferon alfa-2b

Primary outcome measure

Tolerability of combination therapy. A patient is classified as not tolerating treatment if they discontinue either fedratinib or ropeginterferon alfa-2b due to drug-related toxicity, due to delays in treatment exceeding 28 consecutive days due to drug-related toxicity, or if a treatment toxicity-related death is reported, within 4 months of starting combination therapy.

Secondary outcome measures
1. Tolerability of combination therapy throughout the treatment course. A patient is classified as not tolerating treatment as per the definition for the primary outcome.
2. Best overall response, defined to be complete or partial response, assessed using IWG criteria (spleen size assessed by palpation) within 12 and 24 months from starting combination therapy.
3. The highest tolerated dose of ropeginterferon alfa-2b, in combination with fedratinib, achieved by each patient. To be tolerated, the dose must have been maintained for at least one complete cycle.
4. Toxicity, defined as the proportion of patients experiencing any grade ≥3 adverse event, or a serious adverse event of any grade.
5. Overall survival, defined to be time from starting combination therapy to date of death from any cause.
6. Progression-free survival, defined as the time from starting combination therapy to first event or death from any cause. An event here is defined to be any of the following: an increase in bone marrow fibrosis, an increase in spleen size by more than 5cm or transformation to acute myeloid leukaemia.
7. Quality of life, assessed using the MFSAF v2.0 total symptom score at trial entry and at the end of each cycle of treatment
8. JAK2 V617F clone size, measured at trial entry and 3-monthly during treatment.
9. Bone marrow fibrosis, assessed using consensus definitions (Thiele et al. 2005), at trial entry and 6-monthly during treatment.

Overall study start date
09/02/2021

Completion date
30/06/2026

Eligibility

Key inclusion criteria
1. Age 18 or over at trial entry
2. Confirmed diagnosis of JAK2 V617F positive primary or secondary MF, according to WHO 2016 diagnostic criteria
3. Require treatment, as clinically determined by local investigator
4. Intermediate-2 or high risk according to DIPSS, or intermediate-1 according to DIPSS with palpable splenomegaly >5cm
5. Peripheral blood or bone marrow blasts <10%
6. Adequate blood counts: platelets ≥75 x10-9/L, neutrophils ≥1.0 x10-9/L
7. Adequate organ function

Participant type(s)
Patient

Age group

Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
30

Key exclusion criteria
1. Previous treatment with a JAK2 inhibitor or interferon alpha
2. Chemotherapy or biologic therapy within 2 weeks of commencing the trial treatment, or ongoing toxicity relating to prior therapy
3. Blood thiamine concentration below lower limit of normal
4. Active malignancy treated in the last 2 years
5. Pre-existing and uncontrolled thyroid disease, diabetes or autoimmune disease
6. History of severe psychiatric disorder, including severe depression, suicidal ideation and suicide attempt
7. Current severe or uncontrolled cardiovascular disease
8. Previous organ transplantation receiving ongoing immunosuppression
9. Evidence of active HIV, HBV or HCV infection
10. Pregnant and breast feeding patients and those unwilling to use effective contraception

Date of first enrolment
12/09/2022

Date of final enrolment
31/03/2024

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Belfast Health and Social Care Trust
Trust Headquarters
A Floor - Belfast City Hospital
Lisburn Road

Belfast
United Kingdom
BT9 7AB

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road Glasgow
Glasgow
United Kingdom
G12 0XH

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

Study participating centre
Queen's Medical Centre
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Northern General Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Herries Road

Sheffield
United Kingdom
S5 7AU

Study participating centre
Southampton General Hospital
University of Southampton and University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
St James's University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Cardiff & Vale University Lhb
Woodland House
Maes-y-coed Road

Cardiff
United Kingdom
CF14 4HH

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital
Westminster Bridge Road,
London
United Kingdom
SE1 7EH

Sponsor information

Organisation
University of Birmingham

Sponsor details
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researchgovernance@contacts.bham.ac.uk

Sponsor type
University/education

Website
http://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Cure Leukaemia

Funder Name
Celgene

Funder Name
AOP Orphan Pharmaceuticals

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
30/06/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the trial management group by contacting fedora@trials.bham.ac.uk following the end of the study. Each request will be considered on a case by case basis and any research must have the relevant approvals in place. Consent for any future ethically approved research is requested and documented on the Informed Consent Form for the trial.

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
Protocol article		10/01/2025	20/01/2025	Yes	No