

# SPIRIT 3: To evaluate the most effective way to use imatinib, nilotinib and ponatinib in the treatment of chronic myeloid leukaemia

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|----------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>Submission date</b><br>23/07/2013   | <b>Recruitment status</b><br>Stopped   | <input checked="" type="checkbox"/> Prospectively registered<br><input type="checkbox"/> Protocol            |
| <b>Registration date</b><br>01/08/2013 | <b>Overall study status</b><br>Stopped | <input type="checkbox"/> Statistical analysis plan<br><input type="checkbox"/> Results                       |
| <b>Last Edited</b><br>26/09/2016       | <b>Condition category</b><br>Cancer    | <input type="checkbox"/> Individual participant data<br><input type="checkbox"/> Record updated in last year |

## Plain English summary of protocol

Not provided at time of registration

## Contact information

### Type(s)

Scientific

### Contact name

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## Additional identifiers

### Clinical Trials Information System (CTIS)

2012-005696-14

### Protocol serial number

A15810

# Study information

## Scientific Title

A phase 3 randomised non-inferiority trial to evaluate the most effective way to use imatinib, nilotinib and ponatinib in patients with newly-diagnosed chronic phase chronic myeloid leukaemia

## Acronym

SPIRIT 3

## Study objectives

To investigate whether first-line treatment with imatinib (group I) is non-inferior to first-line treatment with nilotinib (group N) when patients on either treatment who are not responding optimally switch to ponatinib. Additionally to investigate whether patients who respond well can subsequently have their treatment reduced and eventually stopped with no adverse consequences.

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Ethics committee approval will be sought via IRAS.

## Study design

Randomised phase III open label non-inferiority trial

## Primary study design

Interventional

## Study type(s)

Treatment

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

Chronic myeloid leukaemia

## Interventions

1. Imatinib - taken as a once daily medication at a dose of 400mg in tablet format. 400mg and 100mg tablets are available to allow dose adjustment.
2. Nilotinib - taken as a twice daily medication at a dose of 300mg (600mg total daily dose) in tablet format. 200mg and 150mg tablets are available to allow dose adjustment.
3. Ponatinib - taken as a once daily medication at a dose of 45mg in tablet format. Ponatinib is supplied as 15mg tablets to allow dose adjustment.

Patients who are eligible will be randomised to receive either imatinib 400mg (Group I) or nilotinib 600mg (300mg BID) (Group N). The treatment allocation will be prepared by the trial statistician and based on a 1:1 ratio between the two arms. Patients who do not respond optimally to these treatments will be switched to ponatinib. Subsequently patients who have received a minimum of 3 years TKI treatment and who have achieved MR3 (BCR-ABL/ABL ratio of 0.1% or less) on any treatment combination and then maintain MR3 or better for a minimum of 2 years will have opportunity to reduce their TKI dose for 12 months and then subsequently cease

TKI treatment altogether.

Patients will be followed up and assessed at the time points outlined in the following Assessment Schedules

1. Schedule - S (Screening/Baseline Schedule) All patients
2. Schedule T (Randomised Treatment) Stage 1 - All Patients
3. Schedule - P (Ponatinib Treatment) Stage 2 Switching patients only
4. Schedule - R (Dose Reduction and Stopping) Stage 3 Eligible patients only
5. Schedule FU (Off Study Treatment Follow-up) Patients who have permanently discontinued study drug before the end of the study.

## **Intervention Type**

Drug

## **Phase**

Phase III

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

Imatinib, nilotinib, ponatinib

## **Primary outcome(s)**

To determine whether, in terms of major molecular response (MMR, MR3) at three years, first-line treatment with imatinib is non-inferior to first-line treatment with nilotinib when patients on either treatment who are not responding optimally switch to ponatinib.

## **Key secondary outcome(s)**

1. To assess survival (OS, PFS and EFS) in group I vs group N at 5 years from study entry.
2. To determine what proportions of patients in group I and in group N who have been on study for at least 3 years and who have achieved stable MR3 for at least 2 years can reduce or stop TKI treatment and maintain at least MR3.
3. To compare the cost effectiveness over a 5 year period (and projected over the lifetime of the patient) of group I vs group N.

## **Completion date**

01/09/2023

## **Reason abandoned (if study stopped)**

Lack of funding/sponsorship

# **Eligibility**

## **Key inclusion criteria**

1. Male or female patients who are 18 years of age or over.
2. Patients must fulfill all of the following:
  - 2.1. Be diagnosed with chronic phase chronic myelogenous leukemia (CML) confirmed by blood morphology and reverse transcriptase polymerase chain reaction (RT-PCR) for BCR-ABL.
  - 2.2. Be enrolled within 3 months of initial diagnosis of chronic phase CML (date of RT-PCR confirming presence of BCR-ABL)
  - 2.3. Be in confirmed chronic phase ie:
    - 2.3.1. Less than 15% blasts in blood (manual differential)
    - 2.3.2. Less than 30% blasts plus promyelocytes in blood

- 2.3.3. Less than 20 % basophils in blood
- 2.3.4. Less than  $100 \times 10^9$  /L platelets
- 2.3.5. No evidence of extramedullary leukaemic involvement, with the exception of hepatosplenomegaly
- 3. Written voluntary informed consent.

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**Key exclusion criteria**

1. Any prior treatment for CML with any tyrosine kinase inhibitors (TKI) (eg imatinib, dasatinib, nilotinib, bosutinib, ponatinib); busulphan, interferon-alpha (IFN-alpha), homoharringtonine, cytosine arabinoside, any other investigational agents.
2. Patients who have received prior CML chemotherapy including regimens used in peripheral blood progenitor cells (PBPCs) mobilisation for haematopoietic progenitor-cell transplantation. (collection of unmobilised PBPCs is allowed at diagnosis).
3. Patients who have had any form of prior haematopoietic stem cell transplant (autograft or allograft).
4. Patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status Score  $\geq 3$
5. Patients with serum bilirubin, SGOT/AST, SGPT/ALT or creatinine concentrations  $> 2.0 \times$  upper limit of normal (ULN)
6. Patients with serum amylase or lipase  $> 1.5 \times$  ULN, history of acute pancreatitis within 1 year of study, history of chronic pancreatitis, or uncontrolled hypertriglyceridaemia (triglycerides  $> 450$  mg/dL)
7. Patients with significant uncontrolled or active cardiovascular disease, specifically including, but not restricted to a) myocardial infarction, unstable angina and/or congestive heart failure within 6 months prior to study; and b) history of clinically significant atrial arrhythmia; or any ventricular arrhythmia.
8. Patients taking medications known to be associated with Torsade de Pointes (eg amiodarone, azithromycin, chloroquine, citalopram, domperidone, erythromycin, quinidine, sotalol, thioridazine)
9. Patients with known uncontrolled hypertension; systolic blood pressure  $> 140$ mm Hg and/or diastolic blood pressure  $> 90$ mm Hg
10. Patients with a known international normalized ratio (INR) or partial thromboplastin time (PTT)  $> 1.5 \times$  ULN, with the exception of patients on treatment with oral anticoagulants, or patients with a known bleeding disorder. Baseline testing of INR is not required.
11. Patients with uncontrolled medical disease such as diabetes mellitus, thyroid dysfunction, neuropsychiatric disorders or infection.
12. Patients who have undergone major surgery within 4 weeks of starting trial investigational

medicinal products (IMP).

13. Patients who are:

13.1. Pregnant

13.2. Breast feeding

13.3. Of childbearing potential without a negative pregnancy test prior to starting trial IMP

13.4. Male or female of childbearing potential unwilling to use barrier contraceptive precautions throughout the trial (postmenopausal women must be amenorrhoeic for at least 12 months to be considered of non-childbearing potential).

14. Patients with a history of another malignancy either currently or within the past five years (with the exception of basal cell skin carcinoma in situ).

15. Patients with a history of non-compliance to medical regimens or patients who can envisage being unable to complete the study for any reason.

16. Patients unwilling to receive trial drug via a home delivery method.

**Date of first enrolment**

01/09/2013

**Date of final enrolment**

01/09/2023

## Locations

**Countries of recruitment**

United Kingdom

England

**Study participating centre**

**Freeman Hospital**

Newcastle-upon-Tyne

United Kingdom

NE7 7DN

## Sponsor information

**Organisation**

Newcastle-upon-Tyne Hospitals NHS Foundation Trust (UK)

**ROR**

<https://ror.org/05p40t847>

## Funder(s)

**Funder type**

Industry

**Funder Name**

ARIAD Pharmaceuticals (USA)

**Alternative Name(s)**

Ariad

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

For-profit companies (industry)

**Location**

United States of America

**Funder Name**

Cancer Research UK (UK)

**Alternative Name(s)**

CR\_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Other non-profit organizations

**Location**

United Kingdom

## Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

**Study outputs**

| Output type                                   | Details                       | Date created | Date added | Peer reviewed? | Patient-facing? |
|-----------------------------------------------|-------------------------------|--------------|------------|----------------|-----------------|
| <a href="#">Participant information sheet</a> | Participant information sheet | 11/11/2025   | 11/11/2025 | No             | Yes             |
| <a href="#">Study website</a>                 | Study website                 | 11/11/2025   | 11/11/2025 | No             | Yes             |