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

Submission date 23/07/2013	**Recruitment status** Stopped	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 01/08/2013	**Overall study status** Stopped	
Last Edited 26/09/2016	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration

Study website
http://spirit3.spirit-cml.org/

Contact information

Type(s)
Scientific

Contact name
Prof Stephen O'Brien

Contact details
Freeman Hospital,
Freeman Road,
High Heaton,
Newcastle-upon-Tyne
United Kingdom
NE7 7DN
0191 282 0904
wendy.banks@ncl.ac.uk

Additional identifiers

EudraCT/CTIS number
2012-005696-14

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
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

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
http://spirit3.spirit-cml.org/

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 measure
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.

Secondary outcome measures
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.

Overall study start date
01/09/2013

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 x 109 /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

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
1000

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 ≥ 3
5. Patients with serum bilirubin, SGOT/AST, SGPT/ALT or creatinine concentrations > 2.0 x upper limit of normal (ULN)

6. Patients with serum amylase or lipase > 1.5 x 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 > 140mm Hg and/or diastolic blood pressure > 90mm Hg
10. Patients with a known international normalized ratio (INR) or partial thromboplastin time (PTT) > 1.5 x 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
England

United Kingdom

Study participating centre

Freeman Hospital
Newcastle-upon-Tyne
United Kingdom
NE7 7DN

Sponsor information

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

Sponsor details
Freeman Hospital,
Freeman Road,
High Heaton,
Newcastle Upon Tyne
England
United Kingdom
NE7 7DN
+44 (0)191 282 0904
meg.buckley@ncl.ac.uk

Sponsor type
Hospital/treatment centre

Website
http://spirit3.spirit-cml.org/contact.aspx

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, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration