SPIRIT 2

A phase III, prospective randomised comparison of
- imatinib 400mg daily
versus
- dasatinib 100mg daily
in patients with newly-diagnosed chronic phase chronic myeloid leukaemia (CML).

SPIRIT 2 CLINICAL TRIAL SUPPLIES

INFORMATION FOR PHARMACISTS

Summary of changes from version 3.0

Change	Detail	Section(s)
1.	Addition of information for sites using generic imatinib	Section 2, page 4
2.	Update to stud drug supply of dasatinib	Section 2, page 4
3.	Update to the location of the Temperature Excursion Response Form	Section 6, page 5
4.	Addition of Post Visit 15 and End of Trial arrangement	Section 12 and 13, page 9
5.	Update to SPIRIT Office Contact Details	Section 14 page 9

Contents

1. About SPIRIT 2

- SPIRIT 2 is a Phase III, multicentre, open-label, prospective randomised trial comparing imatinib (Glivec) 400 mg daily versus dasatinib (Sprycel) 100mg daily in patients with newly-diagnosed chronic phase CML.
- The sample size is 810 patients (405 patients per arm).
- After screening, all patients will be randomised in equal proportions to one of the following two treatment groups: Imatinib 400 mg daily **OR** b) Dasatinib 100 mg daily.
- Both treatments will be started immediately at full dose.
- The primary endpoint is to compare Event Free Survival (EFS) at 5 years.
- Additional endpoints are defined in section 3 of the protocol.
- The Dasatinib will be provided free of charge by Bristol Myers Squib (BMS) until last patient last visit (at least 5 years per patient). There is therefore a net saving of NHS treatment costs of up to 5 years of imatinib for 50% of entrants.
- Further details about the study can be found at www.spirit-cml.org.

2. Study Medication

Further information can be found in section 8 of the protocol.

a) Imatinib

Arm A: The 400mg daily imatinib is supplied from your hospitals own NHS stock.

If protocol v2.1 has been approval locally then generic imatinib can be used in accordance with your local policies. Please add brand of generic to the accountability log of the patients affected.

b) Dasatinib

Arm B: The 100mg daily Dasatinib will be provided free of charge by Bristol Myers Squib until last patient last visit (7th March 2018).

The free Dasatinib supply is guaranteed for 5 years for each patient from the point at which the last patient is randomised into the trial – representing a minimum of 5 years supply per patient at least. At the point of last patient last visit, patients will be transferred onto commercial stock of dasatinib, in accordance with national guidelines.

Clinical Trial Supplies of dasatinib 50mg and 20 mg film coated tablets will be supplied in bottles of 30 tablets directly from BMS. Supplies should be stored at 25°C (see section 6).

3. Labelling

a) Imatinib

Clinical trial labels will need to be applied to the NHS-supplied imatinib commercial stock used for the study. The trial office will supply the labels. The following information will need to be added to the label in the pharmacy: Investigator, Site number, Patient Initials and Trial number and Date of dispensing.

For clinical trial use only. Keep out of reach of children.
SPIRIT 2 EudraCT no. : **2007-006185-15**
Chief Investigator: Dr S. G. O'Brien.
Trial Sponsor: The New castle-upon-Tyne Hospitals NHS Trust.

For oral use only. To be used as directed by your doctor.
Do not store above 30°C.
Investigator:_____ Patient No.:_____
Site ID: _____
Date Dispensed: _____ Patient Initials:_____

Example of imatinib clinical trial label.

b) Dasatinib

The dasatinib will be provided with a BMS clinical trial label and a label identifying the trial and Sponsor (examples available in SPIRIT 2 pharmacy file). Details to identify the site, patient and date of dispensing should be added and this may be done by use of a local dispensing label.

4. Trial Prescriptions

Trial prescriptions are available on the SPIRIT 2 website (www.spirit-cml.org – see ISF, pharmacy section). The prescription can be used as is or can be modified to suit practices at your site. If a modified prescription is used this must be approved by the trial office first. Please contact the Trial Office if you will be using electronic prescribing.

5. Dose reductions

Please refer to section 7 of the protocol for the dose reduction and escalation schedule for use in the management of toxicities.

6. Temperature control

a) Dasatinib

Dasatinib should be stored at 25°C and excursions are permitted between 15-25°C. All excursions outside this range should be notified to the Sponsor Trial Office using the Temperature Excursion Response Form for Investigational Medicinal Products. The current form can be obtained from the SPIRIT 2 website (http://spirit-cml.org/isf/pharmacy/). Stock should be quarantined until you have a decision on continued use for the stock. All paperwork should be filed in the pharmacy file.

Please see section 7.a) below for details of temperature monitoring during shipment and on arrival at site.

b) Imatinib

Imatinib is treated as an IMP from the point at which clinical trial labelling is applied. If imatinib stock has clinical trial labelling applied in advance of dispensing and is stored as IMP it should be held in a temperature controlled area according to the recommended storage conditions. Deviations should be dealt with according to your local procedures, contacting the pharmaceutical company for advice as appropriate. Deviations from the recommended storage conditions for each product should be documented with a description of how this was handled.

7. Receipt of dasatinib

a) TagAlert information

Dasatinib for the SPIRIT 2 trial is sent directly from the manufacturer (Bristol Myers Squibb) to your pharmacy. Dasatinib shipments include a TagAlert™ unit. This is a temperature indicator used to monitor in-transit conditions of Dasatinib. The LCD display will show the status of the shipment in a black bar with **OK**, or numbers **1**, **2**, **3** or **4**.

You will need to record the display results on the packing list received with your Dasatinib shipment. If you see **OK** – the shipment arrived to you without temperature incident and the drug product is acceptable for use. The TagAlert™ unit should be thrown away.

If you see any alarm NUMBER (**1**, **2**, **3** or **4**) – the shipment was exposed to a temperature change that may have been extreme. You should retain the TagAlert unit and notify the Trial Office immediately. Stock should be quarantined.

b) Shipping paperwork

The following will be provided with your shipment and the following actions should be taken:

- Packing list: Complete the confirmation of receipt (including TagAlert status as above). The completed paperwork (*all pages*) should be faxed back to the trial office on 0191 376 0748 and the signed copy retained in your pharmacy file. Duplicate copies may be discarded.
- Batch Release Certificate, Certificate of Analysis, evidence of Use Date Extension (all as applicable): One copy of each should be filed in your pharmacy file. Duplicate copies may be discarded.

c) Receipt log

Each delivery should be recorded on the receipt log as relevant for 50mg or 20mg supplies (logs are available on the SPIRIT website (see www.spirit-cml.org, documents and downloads under pharmacy section).

8. Returns and destruction

Stock can be destroyed in the following circumstances. Appropriate documentation should be maintained and stock does not need to be retained for checking by a Trial Manager/Monitor prior to destruction. All destruction should be carried out according to your normal hospital procedures.

a) Patient returns

Destruction of patient returns should be documented on the individual patient's dispensing and return medication record.

b) Undispensed stock

No undispensed stock should be destroyed without written confirmation from the trial office. Destruction of undispensed drug (e.g. expired stock, stock you have been instructed to destroy following temperature excursion) should be recorded on the destruction log sheet available on the SPIRIT 2 website or held in the pharmacy file. Copies of certificates of destruction should be filed

if these are created as part of normal destruction procedures.

9. Pharmacy Documentation

As a minimum, pharmacy documentation as listed on the pharmacy file Table of Contents provided by the Trial Office will be maintained. This will include:

- Drug Storage Conditions:
  - Documentation of where and how drug will be stored at your site.
  - Documentation of any monitoring systems that are used at your site that will apply to study drug stored at the site.
  - Documentation of any deviations (eg. Temperature) that occur outside the recommended storage conditions for each product and how they were handled (see temperature storage section).
- Drug Dispensing/Returns/Destruction:
  - A log should be kept of all clinical trial supplies received by the pharmacy.
  - A log should be kept of all drugs dispensed, returned and destroyed for the study (see returns and destruction section).
- Labelling QC process:
  - Documentation of how the labelling of the NHS stock imatinib will be QC'd or reference to the relevant hospital procedure.

10. Drug Supply Flow

Dasatinib for the SPIRIT 2 trial is sent directly from the manufacturer (BMS) to your pharmacy. Please ensure that the trial office has the correct pharmacy details (contact, address etc) for your site.

a) Site Activated

When your hospital has received local Trust R&D approval your site will be initiated and activated. This allows your hospital to begin enrolment of patients into the trial. Upon site activation the trial office will send some imatinib trial drug labels to your pharmacy and a float supply of dasatinib 50mg and 20mg tablets will be ordered.

b) Patient Randomised to dasatinib 100mg

Randomisation of a patient to the dasatinib arm automatically triggers a drug supply request for 3 months supply (6 bottles x 50mg tablets).

c) Patient Continuing in Trial

For patients continuing on treatment please complete the dasatinib order form for when you require re-supply stating the number of bottles of dasatinib required at each strength (20mg or 50mg tablets). The order form can be found in your Pharmacy site file and also on the SPIRIT 2 website – Documents and Downloads – Pharmacy Section.

11. Contents of SPIRIT 2 Pharmacy File

A pharmacy file, forming a working part of the ISF will be provided at site set-up. This will be archived with the main site ISF during close down.

12. Study Medication Post Visit 15

a) Imatinib

Trial prescriptions must no longer be used for patients randomised to imatinib post Visit 15.

For patients remaining on imatinib following completion of the trial, please revert to local documentation when prescribing the medication and trial labels should not be used.

If trial prescriptions/labels have been used post Visit 15, please document this error as a file note and file in the SPIRIT 2 Pharmacy Site File.

Accountability for imatinib is no longer required after Visit 15.

b) Dasatinib

Patients are able to remain on trial supply of dasatinib until last patent last visit (7th March 2018). Please continue to use the trial prescription and reorder stock in the usual manner until this point.

13. End of Study Arrangements (Dasatinib)

Trial supply of dasatinib will not be available after last patient last visit (7th March 2018).

After this point, all patients taking dasatinib must stop taking trial supply and move on to commercial supply of the drug.

Orders for trial supply will be accepted prior to last patient last visit, however the number of bottles requested will be checked against the Trial Office records. Any orders over the expected amount will be queried with site to confirm the number of bottles required.

Trial prescriptions must not be used past this point, please revert to local documentation when prescribing the medication.

14. SPIRIT Office Contact Details

Address: Newcastle University
2nd Floor, Biomedicine West Wing
International Centre for Life
Times Square
Newcastle upon Tyne
NE1 4EP

Telephone: 0191 282 0904
Fax: 0191 376 0748

Email: wendy.banks@ncl.ac.uk

Website: www.spirit-cml.org