CONFIDENTIAL

A trial of de-escalation and stopping treatment in chronic myeloid leukaemia patients with excellent responses to tyrosine kinase inhibitor therapy

(**De-Escalation** and **S**topping **T**reatment of **I**matinib, **N**ilotinib or spr**Y**cel in chronic myeloid leukaemia)
(DESTINY)

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Liverpool Cancer Trials Unit

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Trial Protocol Approval

I, the undersigned, hereby approve this clinical trial protocol:

Signature: _____ **Date:** 26/7/2018

Professor Richard Clark
Chief Investigator
University of Liverpool

Signature: _____ **Date:** 17 JULY 2018

Alex Astor
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Signature: _____ **Date:** 26/7/18

Professor Tom Walley
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General Information

This document describes the DESTINY trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Cancer Research UK Liverpool Cancer Trials Unit (LCTU)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via LCTU.

Statement of Compliance

This trial is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004

UK Registration

This trial has National Research Ethics Service (NRES) approval and holds a Clinical Trials Authorisation issued by the Medicines and Healthcare Products Regulatory Agency (MHRA). Each centre must also undergo Site Specific Assessment by the relevant Trust Research and Development department (or Local Research Ethics Committee for Non-NHS Sites) and NHS sites must be granted Research and Development Approval from each Trust where the trial will be carried out.

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Glossary

AE	Adverse Event
AR	Adverse Reaction
BCR-ABL1	The fusion oncogene that causes CML. Its level correlates with disease burden
CI	Chief Investigator
CML	Chronic myeloid leukaemia
CRF	Case Report Form
CTU	Clinical Trials Unit
GP	General Practitioner
IB	Investigator's Brochure
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
IS	International Standard (for reporting molecular blood tests results)
LREC	Local Research Ethics Committee
MREC	Multi-centre Research Ethics Committee
Ph	Philadelphia chromosome
PI	Principal Investigator
(q) PCR	(quantitative) Polymerase chain reaction
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine kinase inhibitor (imatinib, nilotinib or dasatinib)
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 PROTOCOL SUMMARY

Title: **A trial of de-escalation and stopping treatment in chronic myeloid leukaemia patients with excellent responses to tyrosine kinase inhibitor therapy**

(De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in chronic myeloid leukaemia) (DESTINY)

Phase: II

Sample Size: 168 patients from approximately 22 sites across the UK will be recruited from two groups; those with molecularly undetectable disease (the 'MR4' group); and those with stable low level but still detectable BCR-ABL1 (where BCR-ABL1 is consistently below 0.1%; the 'MMR' group).

Main Criteria for Inclusion:

1. CML in first chronic phase.
2. Demonstration of BCR-ABL1 positivity at or shortly after original diagnosis*.
3. Written Informed Consent
4. Must have received TKI treatment for at least 3 years.
5. At least 3 molecular results over the preceding 12 months, that fit either of the following groups (results from any UK lab are acceptable):
    - (MR4 group) all the available BCR-ABL1 molecular results over the preceding 12 months are in MR4 (MR4 is defined as a BCR-ABL1/ABL1 ratio of zero, (reported to international standard (IS) where possible); with at least 10,000 ABL1 control transcripts).
    - (MMR group) some or all BCR-ABL1 molecular results are in MMR (BCR-ABL1/ABL1 ratio of 0.1% or less, (reported to International Standard (IS) where possible), but not zero, with at least 10,000 ABL1 control transcripts). If the results over the preceding 12 months are a mix of MMR and undetectable BCR-ABL1, then the patient is eligible for the MMR but not the MR4 group.

** Patients who are Philadelphia chromosome (Ph) negative (or whose Ph status is not known) are eligible. Patients who do not have a standard BCR-ABL1 fusion transcript (i.e. other than e13a2 or e14a2, also known as b2a2 and b3a2) may be eligible, but*

before screening the patient, contact should be made with Prof Foroni at Hammersmith Hospital (see contacts) since specialised quantitative molecular assessment will be required.

Main Criteria for Exclusion:

1. Age under 18
2. Life expectancy is predicted to be less than 37 months because of intercurrent illness
3. Presence of serious concomitant illness (e.g. heart, renal, respiratory or active malignant disease) that might preclude completion of the trial
4. CML in accelerated phase or blast crisis at any time
5. Any molecular result during the preceding 12 months that is not in either MMR or MR4.
6. Patients who switched previous licensed TKI treatment (imatinib, nilotinib or dasatinib) twice or more because of **intolerance**.
7. Treatment with higher than standard TKI doses ('standard' is defined as imatinib 400mg daily, nilotinib 400mg twice daily or dasatinib 100mg daily). However, an exception is made for patients who at original diagnosis commenced on either 800mg of imatinib on the SPIRIT1 study, or 140mg (or 70mg b.d.) of dasatinib in the Bristol-Myers Squibb 034 study. In each case these latter patients ARE eligible provided they fulfil other molecular criteria, since they do not demonstrate resistant disease.
8. Patients who switched previous licensed TKI treatment (imatinib, nilotinib or dasatinib) because of **resistance.** Patients treated with lower (but at least 50%) than standard TKI doses (as defined in the previous criterion) for tolerance reasons may be included, but will de-escalate to the same doses as for standard dose patients and will be analysed separately, as they could be seen as undertreated.
9. Previous treatment with ponatinib or bosutinib. Patients who received interferon prior to commencing TKI (even if resistant to their interferon) are eligible, provided their response to TKI fits the entry criteria and the use of interferon ceased at least 12 months prior to study entry.
10. Pregnant or lactating women
11. Women of childbearing potential, including women whose last menstrual period was less than one year prior to screening, unable or unwilling to use adequate contraception from trial start to one year after the last dose of protocol therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence.

Number of Sites: Approximately 22, all in the UK

Trial Duration: A maximum of 37 months follow-up per patient

Description of Agent/ Intervention: Imatinib, nilotinib or dasatinib; de-escalated to half the standard dose for 12 months. If on imatinib, the dose should be decreased to 200mg daily; if on nilotinib to 200mg twice daily (which is half the standard dose for second line use, since it is anticipated that the vast majority of nilotinib entrants will be receiving 400mg twice daily because of prior imatinib intolerance); and if on dasatinib then to 50 mg daily.

Outcomes:

Primary:

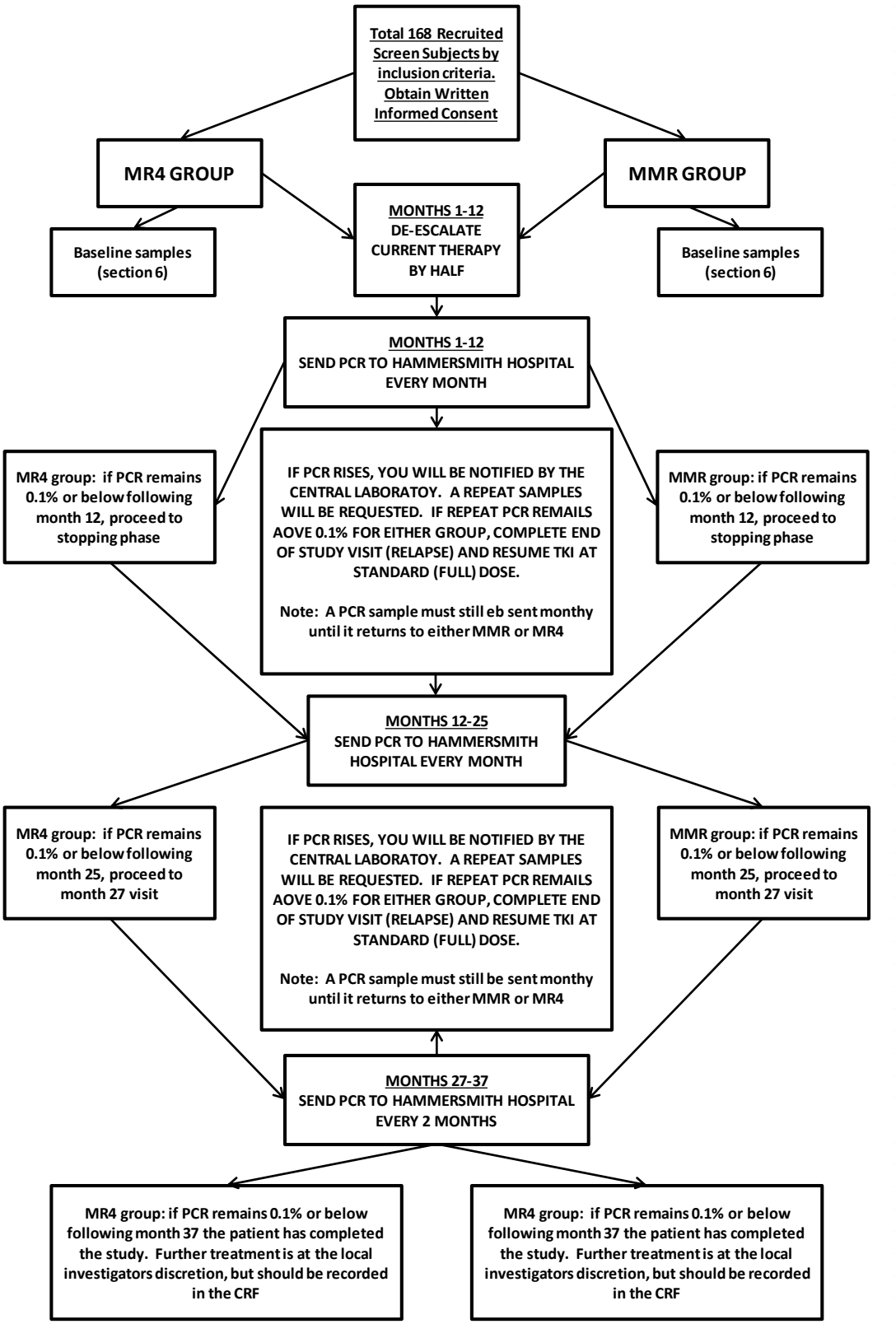
- The proportion of patients who can first de-escalate their treatment (to half the standard dose of their TKI) for 12 months, and then stop treatment completely for a further 2 years, without losing MMR.

Secondary

- Proportion of patients who can successfully de-escalate their treatment (to half the standard dose of their TKI), but who then lose MMR on complete TKI cessation.
- Proportion of patients who lose their MMR on de-escalation/stopping and regain MMR on resumption of their TKI.
- Molecular relapse-free survival (RFS)
- Progression-free survival (PFS)
- Overall survival (OS)
- Event-free survival (EFS)
- Time to MMR recovery (TTR)
- Proportion of registered MMR and MR4 patients in confirmed MR4.5 prior to being enrolled in the study.
- Quality of Life
- Health Economic Assessment
- Lab studies to define subsets of patients who are more likely to relapse on de-escalation / cessation.

Protocol Summary - continued

Figure 1: Schematic of Trial Design:



2 BACKGROUND INFORMATION

2.1 Introduction

About 800 new patients are diagnosed with CML annually in the UK. The vast majority are in the chronic phase at diagnosis, but the disease has a propensity to transform to an acute leukaemia, which is usually fatal. CML treatment was revolutionised about a decade ago by the tyrosine kinase inhibitor (TKI) imatinib. Dasatinib and nilotinib are licensed second generation TKI that are widely used as second line agents for imatinib failure or intolerance, and ongoing trial data suggest that as first line agents they may give more rapid and deeper molecular responses than imatinib[1,2]. Together, these 3 drugs have transformed the outlook for CML from a median survival of about 5 years to one where perhaps 90% of patients are well at 9 years of therapy, and it is predicted that some of these may have a normal life expectancy. Despite its rarity, CML is therefore becoming a common chronic disease in outpatient clinics, since few patients now progress to acute leukaemia.

Response to imatinib and other TKI treatment in CML is assessed according to a series of arbitrary response levels. Within a few weeks of treatment, almost all patients will achieve the first of these, complete haematological response, whereby the blood count and splenomegaly return to normal. The second is clearance of Philadelphia (Ph) chromosome positive cells from the bone marrow, called complete cytogenetic remission, and this typically takes 12-18 months. Patients who do not achieve these two target milestones need treatment modifications, and are not eligible for DESTINY.

Once in complete cytogenetic remission, treatment response is routinely assessed by molecularly measuring BCR-ABL1. BCR-ABL1 is the fusion oncogene that drives CML, and is produced by the Ph chromosomal translocation. The blood BCR-ABL1 transcript level, expressed as a % ratio to normal ABL1 transcripts, reflects the disease burden. In about 50% of patients, the BCR-ABL1/ABL1 ratio remains detectable but very low (0.1% or less). This is termed major molecular response (MMR), and this is internationally used as a response milestone[3]. Once in MMR, the acute leukaemic progression rate is very low; in the IRIS trial of long-term imatinib outcome, in 164 patients achieving MMR at 18 months the subsequent progression rate to acute leukaemia was under 1% at 84 months[4].

After some years of imatinib treatment, BCR-ABL1 transcripts may become undetectable in about 20% of patients, suggesting that some of these may be functionally cured. Since apparent BCR-ABL1 negativity is relative to the volume of the tested sample, it is preferable to describe undetectable transcripts in relation to the number of control (almost always ABL1) transcripts in the sample. Undetectable BCR-ABL1 amongst at least 10,000 control ABL1 transcripts is increasingly used as a more stringent molecular milestone than MMR, and is known as 'molecular response at the 4 log level' or 'MR4' (since 10,000 is equivalent to 4 logs). MR4 is preferable to the term 'complete molecular responders' and is used here. It is therefore possible that after some years of TKI treatment, CML patients in stable MR4 and MMR are being unnecessarily over-treated.

2.2 Rationale

The French STop IMatinib (STIM) trial stopped imatinib in patients treated at any dose for at least 3 years, who had been in sustained MR4 for at least 2 years (confirmed with five BCR–ABL1 analyses during this time). Data on 69 patients with at least 12 months follow up have been published[5]. Updated data on 100 cases presented in September 2012 show that 43% remain free of molecular relapse ('relapse' defined as reappearance of BCR-ABL1) at 18 months and 39% at 24 months. A total of 61 (of 100) cases have had a molecular relapse, of which 59 occurred within the first 7 months off treatment, and one relapse each at 19 and 21 months. Similar data on 35 Australian cases have been presented[6] but not yet published. In a separate retrospective Korean trial[7] stopping imatinib in patients at various response states (some not even in complete cytogenetic remission), all but 2 relapsed. The frequency of molecular monitoring was variable in this trial. Of those in MR4, 3 had cytogenetic relapse and had not returned to MMR by the end of the trial. In a separate ongoing trial in France, 7 of 12 patients in MR4 after first line dasatinib or nilotinib remain in MR4 after at least 6 months off treatment (Réa D, personal communication).

In STIM, the probability of relapse is higher in female patients (though this is less clear on later follow up) and in those with shorter duration of prior imatinib (especially under 48 months). All 61 relapses were advised to recommence imatinib, and 51 of 56 assessable cases were restored to MR4 with a median of 4 months, with the remaining 5 cases all in MMR but with occasionally undetectable BCR-ABL1 (the 5 non-assessable cases opted to delay their recommencement of imatinib; all have also returned to MMR with occasional undetectable BCR-ABL1).

The European LeukaemiaNet is setting up a trial called EUROSKI for excellent CML responders, which is a repeat of the French STIM trial in several hundred patients in MR4 across Europe. Each country will run their own version and results will then be collated centrally.

DESTINY is a pilot for SPIRIT3, the UK national phase III trial in newly diagnosed CML opening during 2013. It is also of pharmaco-economic relevance as the prevalence of CML continues to rise.

2.3 Objectives

The next definitive UK phase III trial in chronic myeloid leukaemia (CML) will be SPIRIT3, which will open in the second half of 2013. This will incorporate a de-escalation and stopping strategy for patients who achieve excellent responses after at least 3 years of treatment with a tyrosine kinase inhibitor (TKI).

DESTINY is to act as a pilot for this strategy in SPIRIT3, by defining the proportion of patients that relapse during 12 months of TKI de-escalation followed by 24 months of cessation. DESTINY also includes scientific bolt-on studies (sections 6.3 and 8.), quality of life assessments and health economic evaluation (sections 4.1 and 8.2.4).

Patients are eligible for DESTINY if in first chronic phase; have been treated with imatinib, dasatinib or nilotinib for at least 3 years from original diagnosis; and whose BCR-ABL1 levels have been at or below 0.1% (reported to IS where possible) on all tests for the past 12 months. Two groups will be studied; those in whom BCR-ABL1 has been undetectable for at least 12 months in at least 3 samples, all of which have at least 10^4 control transcripts (molecular remission at the 4-log level, abbreviated as the ‘MR4’ group), and those in whom BCR-ABL1 is detectable on some or all tests in

the past 12 months, but always below a level of 0.1% (reported to IS where possible) (major molecular response, abbreviated to the 'MMR' group). Both MR4 and MMR groups will be treated identically though analysed separately, by initially de-escalating treatment to 50% of the standard dose for 12 months. If the BCR-ABL1 level remains at or below 0.1% IS, treatment is then completely stopped, and observation continues for a further 24 months.

The objective of DESTINY is to determine the safety and efficacy of initially de-escalating and then stopping TKI treatment, in CML patients with either undetectable disease or with stable MMR.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

The UK NCRI CML subgroup has extensively discussed its strategy for stopping, and has also consulted with patients at the national CML patient day in 2011 and 2012, where a poll suggested that at least 75% of patients wish to decrease or stop their treatment if thought to be clinically safe. The issue is also of interest to the wider NHS, especially as the prevalence of CML continues to rise. Whilst confirmation of French STIM and other studies is important, in view of their high relapse rate we would prefer a more cautious approach, whereby patients first de-escalate TKI treatment for 12 months, to identify patients in whom outright cessation of TKI might rapidly produce molecular relapse. In addition, pilot/anecdotal experience in MMR patients who stop TKI (because of pregnancy or personal preference) suggest that on stopping imatinib, BCR-ABL1 transcripts may remain unchanged for prolonged periods in some patients, and treatment resumption in patients who lose MMR almost always restores molecular response. Some MMR patients may therefore behave similarly to MR4 patients, and they are therefore included in this conservative strategy of initial de-escalation prior to cessation. DESTINY therefore includes not only MR4 patients but also those in enduring MMR, and is designed to harmonise with EUROSKI wherever possible, but to accommodate these aims.

2.4.2 Known Potential Benefits

Imatinib has several mild but persistent side effects such as rash, oedema and GI upsets. Patients differ in their tolerance of these, and their improvement on dose decrease or discontinuation might improve quality of life. Similarly, dasatinib may produce pleural effusions in about 14% of patients, and there are also recent suggestions that dasatinib may produce pulmonary hypertension, and that nilotinib may be associated with an increased late risk of peripheral vascular and ischaemic heart disease. Treatment cessation and de-escalation therefore merit further trial in CML patients with excellent responses to TKI; data are also required on which patients may benefit most.

As the prevalence of CML continues to rise, there is a financial cost of giving unnecessary treatment, since the annual cost of imatinib 400mg daily is £20,980, dasatinib 100mg daily £30,477 and nilotinib 400mg twice daily £20,980 (via the UK patient access scheme) (all prices exclusive of VAT).

It is estimated that DESTINY will bring a substantial **saving** to the NHS. Routine care typically requires 3-monthly molecular monitoring, whereas in DESTINY this will be

carried out monthly for 2 years and then 2-monthly. This means an additional 18 extra visits for molecular tests in DESTINY patients who complete the 37-months of follow-up. However, the hypothesis is that the cost of the extra visits and tests is more than offset by the saving in TKI drug costs. To take a worst case scenario with results worse than the French STIM, whereby 50% relapse at a median of 6 months de-escalation, 50% of the remainder relapse at a median of 6 months of cessation, and the remaining 25% (42 cases) have not relapsed by 37 months, then the strategy will save approximately £4.26 Million. The saving will be increased if the relapse rate is less dramatic than this, or if some entrants are receiving dasatinib rather than imatinib or nilotinib.

3 SELECTION OF CENTRES/CLINICIANS

Each participating Centre (and investigator) has been identified on the basis of:

- Having at least one lead clinician with a specific interest in, and responsibility for, supervising and managing patients with CML.
- Showing enthusiasm to participate in the trial.
- Ensuring that sufficient time, staff and adequate facilities are available for the trial.
- Providing information to all supporting staff members involved with the trial or with other elements of the patient's management.
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the trial, including signing up to Good Clinical Practice (GCP) and other regulatory documentation.

3.1 Centre/Clinician Inclusion Criteria

a. Positive Site Specific Assessment (SSA) by Local NHS R&D offices
b. Local Research and Development (R&D) approval
c. Signed Research Site Agreement
d. Receipt of evidence of completion of (a) & (b) by LCTU
e. Completion and return of 'Signature and Delegation Log' to LCTU
f. Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI)
g. CV including a record of ICH GCP training – Other personnel on the delegation log
h. Clinical Trial Protocol Receipt Form
i. Investigator Brochure's Receipt Form
j. Local laboratory accreditation/Quality Check
k. Local laboratory reference ranges
l. Patient information sheet (PIS), consent form and GP letter on local Trust headed paper

3.2 Centre/Clinician Exclusion Criteria

a. Not meeting the inclusion criteria listed above.

4 TRIAL DESIGN

4.1 Overall Design

This is a phase IIb feasibility trial of TKI de-escalation followed by cessation, in CML in either stable MR4 or MMR. If this strategy has a lower relapse rate than simple cessation (as studied in the French STIM trial and to be expanded in EUROSKI), it will then become part of the 'cessation module' in the next UK phase III trial, known as SPIRIT3. It is anticipated that SPIRIT3 will open in the second half of 2013, though its de-escalation/stopping module does not need to be finalised until 2016/17. The present trial will inform the safety of de-escalation/stopping in MMR patients, the frequency of molecular monitoring, the optimal duration of prior TKI, and whether particular risk groups or laboratory features predict relapse.

The trial consists of 2 groups of CML patients who have had excellent responses to at least 3 years of TKI treatment; firstly those with molecularly undetectable disease (MR4 group) and secondly those with disease at a low and stable level (the MMR group), in each case for at least the preceding 12 months.

168 MR4 and MMR will be recruited in total. MR4 and MMR entrants will be treated identically though will be analysed separately. All will first de-escalate to half the standard first line dose (i.e. imatinib 200mg daily, nilotinib 200mg twice daily or dasatinib 50mg daily) for 12 months. Molecular monitoring will be carried out monthly. 'If that at 12 months remains in MMR (either MR4 or MMR group), then TKI is stopped at the end of month 13 (this allows a month for the 12 month result to be done and reported, and the patient to be seen). Monitoring continues monthly until the end of month 25, then 2-monthly until the end of month 37. See flow chart in Section 1.

At molecular relapse (defined as the loss of MMR on 2 consecutive occasions), TKI should be re-escalated/resumed at standard dose and the patient is off trial, except that samples should still be sent centrally until MMR (or MR4), i.e. BCR-ABL ≤ 0.1% IS, is regained, and the patient should be followed indefinitely for outcome. Although the primary endpoint is the proportion who lose MMR by the end of month 37 (i.e. 2 years of cessation), follow-up continues indefinitely. See flow chart in Section 1.

Quality of life assessment will be assessed at entry and after 1, 2, 3, 6, 9, 12/13, 14, 15, 16, 19, 22, 25, 29, 33 and 37 months. Standard EQ-5D and FACT-BRM questionnaires will be used at each assessment point.

4.2 Primary Endpoint

The primary end-point for both the MR4 and the MMR groups is the proportion of patients who can first de-escalate their treatment (to half the standard dose of their TKI) for 12 months, and then stop treatment completely for a further 2 years, without losing MMR. This will be calculated separately for each of the two groups (MR4 and MMR). BCR-ABL1 will be assessed by standard PCR based molecular monitoring on blood, carried out more frequently than usual. It is not expected that any patient will undergo more serious relapse than loss of MMR.

4.3 Secondary Endpoint(s)

- Proportion of patients who can successfully de-escalate their treatment (to half the standard dose of their TKI), but who then lose MMR on complete TKI cessation.
- Proportion of patients who lose their MMR on de-escalation/stopping and regain MMR on resumption of their TKI.
- Molecular relapse-free survival (RFS). RFS is defined as the time from the first day of de-escalation to the date of confirmed loss of MMR (two consecutive BCR-ABL >0.1% IS).
- Progression-free survival (PFS). PFS is defined as the time from the first day of de-escalation to the date of progression to accelerated phase/ blast crisis or death from any cause (earliest occurrence).
- Overall survival (OS). OS is defined as the time from the first day of de-escalation to the date of death from any cause.
- Event-free survival (EFS). EFS is defined as the time from the first day of de-escalation to the date of confirmed loss of MMR, progression to AP/BC or death from any cause.
- Time to MMR recovery (TTR). TTR is defined as the time from the date of confirmed loss of MMR to the date of MMR recovery.
- Proportion of registered MMR and MR4 patients in confirmed MR4.5 (BCR-ABL ≤ 0.0032% IS with at least 31,623 ABL1 control transcripts) prior to being enrolled in the study (screening phase).
- Quality of Life
- Health Economic Assessment
- Lab studies to define subsets of patient who are more likely to relapse on de-escalation / cessation.

5 TRIAL POPULATION

5.1 Eligibility Criteria

Please refer to section 1, protocol summary, for eligibility criteria.

5.2 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, sample collection, follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-trial evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

Final assessments will be performed (if possible) and should include laboratory samples, and recording concomitant medication. All the results of the evaluations and observations, together with a description of the reasons for trial withdrawal, must be recorded in the CRF.

Patients who are removed from the trial due to adverse experiences (clinical or laboratory) will be treated and followed-up according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.

The following are justifiable reasons for the Investigator to withdraw a patient from the trial:

- unacceptable toxicity
- unforeseen events (any event which in the judgement of the Investigator makes further TKI de-escalation/cessation inadvisable)
- SAE requiring recommencement of TKI treatment
- withdrawal of consent (where the patient is not evaluable, additional patients will be recruited to replace them)
- serious violation of the trial protocol (including persistent patient attendance failure and persistent non-compliance with the de-escalation/stopping strategy)
- withdrawal by the Investigator for clinical reasons not related to the trial strategy
- evidence of disease relapse

If patients withdraw from the trial, all efforts should be made to continue follow-up for outcome, especially relapse.

5.2.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.

A copy of the patient CRFs should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The LCTU should be notified in writing of patient transfers.

5.2.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

a. Patient (or, where applicable, the parent/ legal representative) withdraws consent.
b. Unacceptable toxicity.
c. Intercurrent illness preventing further treatment.
d. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 5.3.3).

5.2.3 Withdrawal from Trial Completely

Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. They may need to reaffirm that they consent to follow-up through usual NHS mechanisms. If the patient explicitly states their wish not to contribute further data to the trial, an End of Trial form should be completed in the CRF.

6 ENROLMENT AND REGISTRATION

6.1 Screening

A log of all potential patients will be kept, including individuals who decide not to participate in or who are found to be unsuitable for the trial.

Screening will be performed for potential trial patients after they have consented to trial participation and signed the informed consent form.

If a patient is screened - regardless of whether or not they are entered to the trial – their details should be entered onto the on-line screening form at the LCTU website:

http://www.lctu.org.uk/home/index.asp

Prior to trial entry the following assessments are required:

- The history of the patient's CML and its treatment are required, together with all the available cytogenetic and molecular PCR (BCR-ABL1) results since diagnosis. These **must** include:
    - A minimum of 3 BCR-ABL1 molecular results in the 12 months prior to trial entry* (since these define whether the patient is in the MR4 or the MMR group). Please see sections 1 and 5.1 for details.
- Details of other clinical conditions and concomitant medications are also required, together with an appropriate physical examination.

Pre-registration assessments **must** be performed within 28 days prior to the start of de-escalation.

* Local molecular results from any UK laboratory will define entry

6.2 Enrolment/ Baseline

Patients who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be enrolled on the trial by the LCTU.

To ensure essential entry criteria are fulfilled, enrolment can only occur following the completion and forwarding of the trial registration documents by the investigators:

- Inclusion and Exclusion Criteria
- Registration and screening forms
- Signed Consent form

The registration documents should be faxed or emailed to the LCTU on Monday - Friday from 09:00 to 17:00, fax number: 0151 794 8931. Prior to sending documents, site staff should telephone 0151 795 5479 to inform the LCTU staff of the incoming registration fax or to ascertain the email address.

Registration – Tel: 0151 795 5479 Fax: 0151 794 8931
(Note that the LCTU is open from 09:00 – 17:00, Monday – Friday, excluding public holidays)

6.3 Samples

Laboratory studies to monitor disease response to de-escalation and stopping treatment are an integral and essential part of DESTINY. Additional scientific studies aim to identify factors that predict successful de-escalation/stopping.

Local molecular results from any UK laboratory will define entry, but baseline and all prospective molecular monitoring will be done centrally at Imperial College London, Hammersmith Hospital (Hammersmith), supervised by Prof Foroni (see section 6.3.1 and 3 and Contact Details: Individuals).

All samples should be sent on Monday –Wednesday only.

6.3.1 Samples required

The samples required for external despatch are summarised in Table 1, below. All patients require bone marrow sending to Glasgow Clinical Laboratory and blood to Hammersmith Hospital Clinical Laboratory.

Patients recruited and treated at the Royal Liverpool University Hospital ONLY also require a blood sample to be sent to the Liverpool laboratories.

Table 1: Summary of external sample requirements, timing and destinations

Laboratory	**Diagnosis**	**Screening**	**Subsequent scheduled visits** (monthly until month 25, then 2-monthly until month 37)	**At relapse or month 37** (whichever is the sooner)
GLASGOW	Not needed	1-2ml Bone MARROW in green (heparinised) tube or mauve/purple (EDTA) tubes	Not needed	1-2ml Bone MARROW in green (heparinised) tube or mauve/purple (EDTA) tubes (Relapse ONLY)
HAMMERSMITH	Sample of original diagnostic blood, can be sent after de-escalation has commenced. Site to provide kit/postage.	3 x 6ml (i.e. 18ml) BLOOD into mauve/purple (EDTA) tubes	3 x 6ml (i.e. 18ml) BLOOD into mauve/purple (EDTA) tubes	3 x 6ml (i.e. 18ml) BLOOD into mauve/purple (EDTA) tubes. In relapsing patients resuming full standard dose treatment, please continue to send samples at monthly intervals until MMR (or MR4), i.e. BCR-ABL ≤ 0.1% IS, is regained.
LIVERPOOL (only required for patients recruited at Royal Liverpool University Hospital)	Not needed	30ml blood collected in a Universal Container with preservative free heparin	Not needed	Not needed

Glasgow (all patients)
At trial entry and molecular relapse bone marrow samples are requested to examine the proportion of leukaemic colonies. RNA will also be stored at entry and relapse for later microarray analysis to identify a gene signature associated with relapse. Molecular relapse bone marrow samples should still be requested even if a sample at trial entry was not available.

A quantity of bone marrow should be taken according to local practice, with 1-2 ml collected in either the green topped, heparin-containing tube or the mauve/purple (EDTA) tube (whichever is provided in the kit) and sent overnight (morning delivery) directly to the analysis lab for immediate processing. It is **imperative** that the analysis lab receives adequate (at least one day's) notice that clinical samples are being shipped, to ensure that the appropriate resources are available and ready upon sample delivery. Samples should therefore be despatched on Monday–Wednesday, so as to arrive at the analysis facility on a weekday (Tuesday-Friday).

Hammersmith (all patients)
An **initial sample** to this central laboratory for molecular monitoring is required to assess the level of BCR-ABL1 at trial entry.
Samples to assess the level of BCR-ABL1 by conventional RT-PCR are then required **at each scheduled visit**. Three 6ml (i.e. 18ml) of blood into the mauve/purple (EDTA) tubes are required; these tubes are labelled 'DESTINY' and provided in the sample kits for the trial. These should be collected on a Monday, Tuesday or Wednesday only (to allow them time to arrive at the analysing laboratory before the weekend). Each tube should be clearly marked with the patient's DESTINY trial number, initials, date of birth and the date and time of the sample. Each sample should be accompanied by a DESTINY PCR shipping form.
These samples should continue to be sent at each scheduled visit until relapse and at monthly intervals thereafter until MMR (or MR4), i.e. BCR-ABL ≤ 0.1% IS, is regained.
Note that there is no cost to the investigational site for these molecular analyses.

For all patients, the level of BCR-ABL1 will also be assessed by more sensitive DNA-based PCR. This requires **an additional sample <u>from original diagnosis</u>**, though this should not be sent at trial entry and should follow after the patient has commenced de-escalation. Hammersmith Hospital is happy to liaise about sample details with the local molecular monitoring lab. The contact details are Prof Letizia Foroni, as in section 6.3. Sites will need to provide the kit components for this sample, in discussion with Prof Foroni's team, and arrange postage themselves.

Liverpool (for Royal Liverpool University Hospital patients ONLY)
Samples for Liverpool studies are only required from patients recruited and treated at the Royal Liverpool University Hospital. At trial entry a blood sample is required to examine immune responses to CML (Liverpool). 30ml blood should be collected in a Universal Container with preservative free heparin and sent to Gemma Austin or Alison Holcroft in the Haematology 2nd floor lab. Samples should be despatched on Monday–Thursday, so as to arrive in the Liverpool laboratory on a weekday (Tuesday-Friday).

6.3.2 Sample Kits

Sample boxes (postage pre-paid) will be provided by the LCTU, containing the necessary sample tubes and paperwork for both blood and bone marrow at trial entry, for blood at the subsequent scheduled visits, and for bone marrow at relapse.

LCTU will not supply sample kits, paperwork or pre-paid postage boxes for the additional original diagnosis sample.

6.3.3 Laboratory Contact Details

LIVERPOOL (for patients recruited at the Royal Liverpool University Hospital only)
Mrs Gemma Austin Tel +44(0)151-706-4326
Dept of Haematology email: gemmajon@liverpool.ac.uk
Royal Liverpool University Hospital
Prescot St
LIVERPOOL
L7 8XP

GLASGOW

Ms Heather Morrison Tel: 0141 301 7880
Paul O'Gorman Leukaemia Research Centre e-mail: heather.morrison@gla.ac.uk
Institute of Cancer Sciences
University of Glasgow
21 Shelley Road
Gartnavel General Hospital
Glasgow G12 0ZD

HAMMERSMITH - the package should be clearly marked 'DESTINY trial', and send by 1st class post to

Prof Letizia Foroni, MD PhD FRCPath
Consultant Scientist
Imperial Molecular Pathology Laboratory Tel: 0208 383 2179
G Block, Level 2, room 313 Office: 0208 383 2167/2177
North Corridor FAX 0203 313 1507
Hammersmith Hospital email: l.foroni@imperial.ac.uk
Du Cane Road
London W12 0HS

7 TRIAL TREATMENT/S

7.1 De-escalation phase (12 months)

Patients in both the MR4 and the MMR groups will be treated identically. During the de-escalation phase, all patients (irrespective of their dose at entry) will decrease to half the standard dose of their TKI. It is advised that drug should be dispensed monthly during the 12-month de-escalation phase.

Table 2: Trial drug doses

TKI	De-escalated dose	Frequency
Imatinib	200mg	Once daily
Nilotinib	200mg*	Twice daily
Dasatinib	50mg	Once daily

*This is half the standard dose for second line use, since it is anticipated that the vast majority of nilotinib entrants will be receiving 400mg twice daily because of prior imatinib intolerance. Patients receiving nilotinib as first line therapy should also receive 200mg twice daily in the de-escalation phase, regardless of dose prior to de-escalation.

7.1.1 Formulation, Packaging, Labelling, Storage and Stability

Please refer to the appropriate summary of product characteristics (SmPC):
Glivec 100mg film-coated tablets (imatinib mesilate)
Tasigna 200mg hard capsules (nilotinib hydrochloride monohydrate)
Sprycel 100mg film coated tablets (dasatininb monohydrate)

IMP will be supplied from local site supplies. All IMP management will be conducted as per local site standard conditions

7.1.2 Preparation, Dosage and Administration of Trial Treatment/s

Please refer to the appropriate summary of product characteristics (SmPC) for each IMP

.
Doses are specified in section 7.1 (table 2) of the Protocol.

The reduced study dose is managed by local PI's for all patients on DESTINY. The patient's prescription will be reduced as per table 2.

The local site pharmacy will manage all aspects of dispensing, returns and labelling.

7.1.3 Dose Modifications

Because of the nature of the trial design, dose modifications are not appropriate. If during de-escalation phase a patient requires a different dose to that listed in Table 2, the local investigator should contact the DESTINY trial coordinator who will request further advice from the CI. If the CI cannot make a definitive decision after discussion with the local PI, the matter can be taken to the TMG.

Patients whose molecular monitoring has not changed by 12 months of de-escalation (i.e. remaining undetectable in the MR4 group, or remaining within MMR for the MMR group) will stop therapy. Since time is required to test the 12-month sample, relay the result to the clinical site and for the patient to be seen, the date at which the patient actually stops their treatment is deemed as the month 13 visit.

7.2 Accountability Procedures for Trial Treatment

There is no requirement to maintain drug accountability logs for trial related purposes.

IMPs are administered according to their licensed indication and form.

If treatment is supplied through routine prescribing practices involving, for example community pharmacies or a Homecare provider, these organisations may continue to dispense IMPs once the patient begins de-escalation provided that the local PI approves.

7.3 Assessment of Compliance with Trial Treatment/s

Data regarding dose of treatment prescribed and taken at home will be recorded on the CRF, thus allowing assessment of compliance with the treatment regimen. Data relating to any alteration in symptoms (which may be related to TKI de-escalation/stopping) are also recorded in the drug diaries and the CRF. At the start of each treatment cycle, patients will be issued with treatment diaries to record compliance with home treatment regimens and asked if they had any difficulties with the previous cycle of treatment.

7.4 Concomitant Medications/Treatments

There are no restrictions on concurrent medications or treatments.

7.4.1 Data on Concomitant Medication

Dose and names of all concomitant medication should be documented on the CRF from screening. This will be reassessed by the PI throughout trial participation during clinical review. Any new medications introduced or changes to medications during the trial period should be documented on the CRF.

7.5 Co-enrolment Guidelines

Patients in the DESTINY trial should not be recruited into other studies of anti-CML treatment prior to disease progression. Similarly, patients already participating in other trials of anti-CML therapy should not enter the DESTINY trial.

Individuals already participating in a trial testing a medicinal product unrelated to CML will not be excluded from the DESTINY trial. However, patients in the DESTINY trial will not be allowed to enter other trials, even if these do not involve anti-CML therapy.

Any queries should be addressed to the trial coordinator.

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule of Trial Procedures

Table 3: Schedule of Assessments and Trial Procedures

Procedure	Screening[%]	Baseline[%]	Hammersmith Alert[∞]	Month (i.e. 1 calendar month +/- 7 days, and not 4 weeks)																																At relapse	After Relapse[@]	12 Months after study end (withdraw or relapse)
				1	2	3	4	5	6	7	8	9	10	11	12[&]	13[&] (0*)	14 (1*)	15 (2*)	16 (3*)	17 (4*)	18 (5*)	19 (6*)	20 (7*)	21 (8*)	22 (9*)	23 (10*)	24 (11*)	25 (12*)	27 (14*)	29 (16*)	31 (18*)	33 (20*)	35 (22*)	37 (24*)			
Written Informed consent	X																																				
Confirmation of diagnosis	X																																				
Demographic Data	X																																				X
Medical History	X																																				
Weight, Physical Examination and Vital Signs	X		X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	X Δ	
Prior Treatment for CML	X																																				
Past and present disease status	X																																				
Concomitant disease and treatment	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pregnancy test (in women of child bearing potential only)	X ^																																				
Laboratory Tests (Haematology and Biochemistry)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Additional original diagnostic blood sample to Hammersmith	X#																																				
Blood Samples for BCR-ABL1 to Hammersmith		X [$]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Bone marrow samples to Glasgow		X [€]																																	X		

Blood samples to Liverpool (Liverpool patients only)		X [$]																															X			
Quality of Life assessments (EQ-5D & FACT-BRM)		X [$]	X	X	X	X			X			X			X	X	X	X	X			X			X			X		X		X		X			
Patient diary /symptoms			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
12 Month TKI stopping CRF																												X									

[%] Within 28 days prior to commencing de-escalation unless otherwise stated
^ Within 14 days prior to commencing de-escalation
[#] Can be sent after patient has commenced de-escalation, see section 6.3.1
[$] Within 7 days prior to commencing de-escalation
[€] Within 1 calendar month prior to commencing de-escalation
∞ Will only occur if BCR-ABL elevates to >0.1% IS
[Δ] Weight only
[&]The BCR-ABL1 molecular result at 12 months will determine whether the patient proceeds to stop therapy. 1 month is allowed to perform this test, relay the result to the local team and then see the patient. Therefore the date on which the patient stops their TKI is taken as the month 13 visit, though this may not be exactly 13 months from trial entry.
* Months after stopping treatment appear in brackets
[?] Unless already relapsed
[@] At monthly intervals until MMR, i.e. BCR-ABL ≤ 0.1% IS, is regained.

8.1.1 Screening Assessments

Screening assessments must be performed before a patient is registered for the trial. Please refer to Table 3 for a specific list of assessments. After patients have consented to trial participation and signed the informed consent form, they will be assessed for their eligibility for entry into the trial. Patients who fulfil the entry criteria will be registered. De-escalation must be commenced within 28 days of tests performed at screening (except for pregnancy test which must be within 14 days of de-escalation starting).

At trial entry, the history of the patient's CML and its treatment are required, together with all the available cytogenetic and molecular PCR (BCR-ABL1) results since diagnosis (reported to IS where possible). These **must** include a minimum of 3 BCR-ABL1 molecular results in the 12 months prior to trial entry, since these define whether the patient is in the MR4 or the MMR group; please see inclusion criteria in sections 1 and 5.1 for details. Details of other clinical conditions and concomitant medications are also required, together with an appropriate physical examination (including spleen size and ECOG status).

8.1.2 Baseline Assessments

Baseline assessments must be performed before a patient begins de-escalation. Please refer to Table 3 for a summary of baseline assessments. It is permissible for baseline assessments to be performed at the same time as the screening assessments if they are part of standard care. The following baseline assessments should be performed:

- Laboratory Tests (within 28 days prior to starting de-escalation):
    - **Full Blood Count** (Haemoglobin; White Blood Cells; Neutrophils; Lymphocytes; Monocytes; Eosinophils; Basophils; Platelets
    - **Serum Biochemistry** (Urea; Creatinine; Bilirubin; ALT *or* AST; γGT)
- Blood sample for PCR testing for BCR-ABL1 sent to Hammersmith Hospital (within 7 days prior to starting de-escalation). DESTINY aims to trial the effect of treatment de-escalation/stopping on the disease burden, as assessed by standard BCR-ABL1 monitoring by quantitative PCR. Local PCR results are adequate for defining trial entry, but all subsequent the testing for BCR-ABL1 is centralised at Hammersmith Hospital (see section 6.3 for further details)
- Samples for scientific tests Blood sample to Liverpool (patients recruited at Royal Liverpool University Hospital only) and bone marrow sample to Glasgow (see section 6.3 for further details)
- Quality of life assessments

8.1.3 Planned assessments during de-escalation follow-up phase (1-12 months)

Please refer to Table 3. Once treatment de-escalation is begun, the cardinal investigation is the molecular monitoring of BCR-ABL1 (reported to IS). This is centralised at Hammersmith Hospital, supervised by Prof Foroni, and should be carried out monthly for the 12 months of the de-escalation. Note that for this purpose, 1 month = 1 calendar month and not 4 weeks; although an actual date within one week either

side of the exact monthly calendar date is permissible. The actual monthly evaluation date should be recorded in the CRF.

Once the sample after 12 months of de-escalation is taken, the trial clock pauses while this sample is analysed, the result is relayed to the clinician and the patient is seen. This pause is likely to be about 4 weeks and should not exceed 6 weeks for any reason. During this pause the patient should remain on their de-escalated dose.

Assuming that this 12-month sample shows stable disease (i.e. the PCR result remains at or below 0.1% IS for both the MR4 and the MMR groups), the clock restarts as the 'month 13' visit and the patient should discontinue treatment altogether. Centralised molecular monitoring of BCR-ABL1 (reported to IS) continues monthly for a further 12 months (i.e. to month 25), then 2-monthly until month 37. Section 6.3 summarises the details for the sending of all samples at all time points.

In the particular case where BCR-ABL1 molecular monitoring from entry until month 11 has remained at or below 0.1% IS, but the month 12 sample shows a level above 0.1% IS, the clock remains paused and another sample should be sent for molecular monitoring (called 'Hammersmith ALERT'). If this is also above 0.1% IS then the patient fulfils the definition of relapse, and should resume their full dose of TKI treatment; they should **not** proceed to complete discontinuation.

8.1.4 Planned assessments during 'stopping' follow-up phase (13-37 months)

Please refer to Table 3. The duration of formal follow-up is 37 months. Patients should be seen monthly for the first 12 months of complete cessation, and thereafter 2-monthly. It is assumed that one month is required to test the 12-month sample, relay this to the clinical site and for the patient to be seen. The date at which the patient actually stops their treatment is therefore deemed as the month 13 visit.

Once the patient reaches the month 37 time point, formal monitoring can discontinue and no further trial-specific tests are required; the patient can then be followed according to local practice. Follow-up for outcome is however still required beyond month 37, until 5 years from trial entry; this should include all local PCR results and any requirement for further CML treatment. Details should be entered in the CRF.

8.1.5 Planned assessment at relapse

Please refer to Table 3. Relapse in this trial is defined as a BCR-ABL1/ABL1 ratio assessed by quantitative PCR (i.e. BCR-ABL1 level) measured centrally at the Hammersmith Hospital which rises above 0.1% IS on two consecutive occasions. Baseline samples are not included in the establishing of relapse. It is stressed that this definition of relapse is actually the loss of molecular response, and quite different from more serious relapse such as loss of cytogenetic response, overt haematological relapse or disease progression. The likelihood of any of these latter serious events is seen as exceptionally unlikely (no such events have been observed in any of the 61 relapsing cases in the French STIM trial).

Given this conservative definition of relapse, it is envisaged that overall a substantial proportion of patients will relapse, and not complete trial treatment.

Any sample showing a rise in BCR-ABL1 to > 0.1% IS will prompt an individual call/email to the local site, stressing the importance of the next sample for that patient. If this rise occurs during the final year of trial, where follow-up is normally alternate months, an additional visit (designated 'Hammersmith ALERT') will become mandatory, timed at 1 month after the last visit. If the subsequent sample also shows a BCR-ABL1 level of > 0.1% IS, then the patient has relapsed. The patient should then be recalled promptly, and should resume the full dose of the TKI that they were receiving at trial entry.

At this visit, samples should be sent as in Table 3 (and see Table 1 for sample destinations). This includes a repeat bone marrow, partly for repeat sampling to Glasgow (to monitor changes in primitive leukaemic colonies, as given in section 6.3; please note the requirement to notify Glasgow prior to shipment), and partly for routine standard investigations at local discretion (e.g. to confirm continuance of chronic phase morphologically and cytogenetic remission by G-banded cytogenetics). Details should be entered in the 'relapse' section in the CRF, including additional local bone marrow investigations for morphology and cytogenetics. The patient is then 'off trial' and further treatment decisions can be made according to local practice; however these should be recorded in the CRF under 'after relapse', and centralised monitoring at the Hammersmith Hospital continues at monthly intervals as required, until MMR (or MR4), i.e. BCR-ABL ≤ 0.1% IS, is regained.

8.1.6 Scheduled collection of Samples

Please refer to Tables 1 and 3 and section 6.3.

8.2 Procedures for assessing Efficacy

8.2.1 Trends in molecular monitoring of BCR-ABL1

Local molecular results for BCR-ABL1 (reported to IS where possible) are acceptable to define trial entry, though a sample should be sent at trial entry to Hammersmith Hospital, the site for centralised monitoring.

All centralised Hammersmith Hospital results shall be entered directly onto the LCTU database by their staff. Local results are recordable in the CRF for post month 37 only.

A relapse date is defined as the first of 2 consecutive molecular monitoring tests in excess of 0.1% IS. This date together with the molecular monitoring data should be recorded in the CRF.

8.2.2 Response to recommencing treatment after relapse

Patients who relapse are 'off protocol' and can be treated according to their physician's discretion, but it is strongly recommended that all patients will resume their previous

TKI at the standard dose. After relapse, monthly monitoring samples should still be sent to Hammersmith Hospital for centralised molecular monitoring for BCR-ABL, until MMR (or MR4), i.e. BCR-ABL ≤ 0.1% IS, is regained. This is to document the kinetics of return to MMR/MR4. Details should be recorded in the 'after relapse' section of the CRF.

8.2.3 Quality of Life Assessments and Patient Diaries

All documents in this section are available for download from the LCTU website http://www.lctu.org.uk. To ensure current versions are used, please print directly from the LCTU website as and when they are needed.

Quality of Life Assessments

Either de-escalation or complete cessation of TKI therapy (or both) may alter the patient's quality of life. This will be investigated using standard EQ-5D and FACT-BRM questionnaires at 1, 2, 3, 6, 9, 12 and 13, 14, 15, 16, 19, 22, 25, 29, 33 and 37 months after commencing de-escalation. These timings will coincide with planned attendances. At each of these visits, the patient should complete the questionnaires while at the hospital; they should not take them home.

Note that questionnaires are required at both the 12 month and the 'month 13' visit. This is because the 12 month questionnaire will give the results of 12 months of de-escalation, while the 'month 13' questionnaire will serve as the baseline for the stopping phase.

Patient Diaries

Patient diaries should be completed during the entire de-escalation and stopping phases and any alteration in symptoms (which may be related to TKI de-escalation/stopping) recorded.

8.2.4 Health Economic Assessment

Patients suitable to enter DESTINY would normally typically attend outpatients 3-monthly, for BCR-ABL1 molecular monitoring and repeat TKI prescription, plus maybe a blood count and biochemical profile including liver function testing. In DESTINY, attendance is required monthly for 2 years and then alternate months for a further year. This is an additional 18 visits and 18 BCR-ABL1 molecular monitoring tests over and above that delivered to the typical patient not contemplating de-escalation/stopping. However, this excess cost may be offset by the saving on TKI expenditure as the patient comes off treatment.

DESTINY entrants are generally well, maybe asymptomatic, and do not require inpatient episodes. Resource utilisation analysis is therefore envisaged to be straightforward, and can be based on the data recorded in the CRFs as set out in sections 7 and 8.1. This aspect of the trial will be supervised by Dr Alan Haycox (see contact details at start of protocol).

8.2.5 Laboratory based studies

Laboratory studies should be carried out at trial entry and at relapse (where this occurs). RNA will be stored at entry and relapse, to identify a gene signature associated with relapse, and the immune response to CML will also be examined.

Whether the more sensitive DNA-based BCR-ABL1 assessment predicts relapse will be investigated for MR4 patients where genomic DNA from original diagnosis is available. This will be led by Prof Letizia Foroni, Imperial College London, Hammersmith Hospital. This technique may be more sensitive than conventional RT-PCR.

Finally, the bone marrow sample at entry (and relapse) will be used to examine the proportion of leukaemic colonies by BCR-ABL1 FISH on replate assays from bone marrow colony forming assays (led by Prof Mhairi Copland, Glasgow).

8.3 Procedures for Assessing Safety

Safety will be assessed through the reporting of serious adverse events as described in Section 10.

8.4 Quality of Life and Health Economics

Quality of life assessment will be assessed at entry and after 1, 2, 3, 6, 9, 12/13, 14, 15, 16, 19, 22, 25, 29, 33 and 37 months. Standard EQ-5D and FACT-BRM questionnaires will be used at monthly intervals initially, decreasing subsequently.

Amelioration of symptoms during the de-escalation and/or stopping phases will be captured in the patient drug diaries, which ask patients to record any alteration to symptoms experienced at baseline.

8.5 Substudies

No sub-studies are planned.

8.6 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the trial centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the patient's GP will be asked to provide follow-up information to the recruiting centre.

8.7 Trial Closure

Investigators will be informed when patient recruitment is to cease.

Trial enrolment may be stopped at a site when the total requested number of subjects for the trial has been obtained.

The Independent Safety and Data Monitoring Committee (ISDMC) may recommend to the Trial Steering Committee (TSC) that the trial be stopped prematurely. Such premature termination/suspension of the trial will be notified to the MHRA and MREC as required.

The trial will be considered formally “closed” when the database is locked.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

An overview of the statistical considerations relevant for the trial is included. A single analysis plan will be developed prior to the first planned interim analysis. This analysis plan will contain all information required for all interim analyses and the final analysis of the data. This document will be approved by the trial steering committee and an Independent Safety and Data Monitoring Committee (ISDMC).

For any statistical analysis MR4 patients will be re-classified to either MMR or MR4 group based on the following criterion:

- MR4: At least complete molecular remission MR4 (either (i) detectable disease ≤0.01% BCR-ABL IS or (ii) undetectable disease in cDNA with ≥ 10,000 ABL or ≥ 24,000 GUS transcripts) for at least one year; at least three PCR-results with MR4 within the last year (+- 2 months) before study entry and no PCR-results > 0.01% during the same period.

This is required because:

- The MR4 group definition described in the eligibility criteria is not up-to-date with technological advances in PCR methods; new methods can detect very low levels of residual disease (<0.01%).
- We want to provide comparable results with other major similar trials, and thus we decided to harmonise the MR4 group definition with EUROSKI trial.
- To avoid causing any unnecessary confusion to the sites we decided to keep the initial definition in the eligibility criteria.

9.2 Outcome Measures

9.2.1 Primary

The primary end-point for both the MR4 and the MMR groups is the proportion of patients who can first de-escalate their treatment (to half the standard dose of their TKI) for 12 months, and then stop treatment completely for a further 2 years, without losing MMR. This will be calculated separately for each of the two groups (MR4 and MMR).

9.2.2 Secondary

Secondary endpoints are:

- Proportion of patients who can successfully de-escalate their treatment (to half the standard dose of their TKI), but who then lose MMR on complete TKI cessation.
- Proportion of patients who lose their MMR on de-escalation/stopping and regain MMR on resumption of their TKI.
- Molecular relapse-free survival (RFS). RFS is defined as the time from the first day of de-escalation to the date of confirmed loss of MMR (two consecutive BCR-ABL >0.1% IS).

- Progression-free survival (PFS). PFS is defined as the time from the first day of de-escalation to the date of progression to accelerated phase/ blast crisis or death from any cause (earliest occurrence).
- Overall survival (OS). OS is defined as the time from the first day of de-escalation to the date of death from any cause.
- Event-free survival (EFS). EFS is defined as the time from the first day of de-escalation to the date of confirmed loss of MMR, progression to AP/BC or death from any cause.
- Time to MMR recovery (TTR). TTR is defined as the time from the date of confirmed loss of MMR to the date of MMR recovery.
- Proportion of registered MMR and MR4 patients in confirmed MR4.5 (BCR-ABL ≤ 0.0032% IS with at least 31,623 ABL1 control transcripts) prior to being enrolled in the study (screening phase).
- Quality of Life.
- Health Economic Assessment.
- Lab studies to define subsets of patients who are more likely to relapse on de-escalation / cessation.

All secondary endpoints will be calculated separately for each of the two groups (MR4 and MMR). Safety variables will be summarised by descriptive statistics. SAEs occurring during the 37-month de-escalation and stopping phases will be reported, summarised by incidence rates and classified by the worst observed severity grade. Laboratory data will be presented by day from commencement of de-escalation or stopping. For biochemical investigations, values outside normal limits will be identified and summarised by frequency distribution.

9.3 Sample Size

Seventy cases will give a 90% confidence interval of maximum width 0.2, for a wide range (0.3 to 0.7) of values of the proportion, p, of relapsing patients. The width will be smaller the closer the estimate is to 0 (or 1). Assuming a dropout rate of 17% and an anticipated equal group allocation, 168 patients are needed.

The accrual of patients within each group largely depends on factors that cannot be controlled or specified a-priori. Hence, to avoid early closing of recruitment in one group which could potentially have a negative effect in overall recruitment and would require substantial extension in the recruitment period we are willing to allow for unequal group allocation and some variation in the maximum confidence interval width. Assuming that we recruit 168 patients in total, under the worst case scenario (p=0.5, group allocation 1:3) the 90% confidence intervals for the two groups (“larger” and “smaller”) will have a maximum width of 0.16 and 0.28 respectively.

9.4 Interim Monitoring and Analyses

The proportion of relapsing patients will be assessed at 3 planned interim analyses: when 60 patients relapse or complete 12 months de-escalation, when 60 relapse or complete 12 months of cessation, and when 60 relapse or complete 24 months cessation. There are no formal stopping rules but the Independent Data Monitoring

and Safety Committee (ISDMC) will review the interim analyses and give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. The entire trial (or the MMR or MR4 elements alone) may be stopped if de-escalation or stopping are producing an unacceptable rate of molecular relapse. For this purpose, the MMR and MR4 groups will be treated separately, since the former may well have a higher relapse rate. Unacceptable relapse for this purpose is at the discretion of the Data Monitoring Committee, bearing in mind that the relapse rate in the STIM trial was 61% overall and 59% (48% - 71%) after 12 months of cessation.

Regardless of the reason(s) for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented. In terminating the trial, the sponsor and the Investigators will ensure that adequate consideration is given to the protection of the patient's interest.

All interim analysis results of the primary and secondary outcome measures will be confidential to the ISDMC members and will not be for review by the trial management group (except the trial statistician preparing the ISDMC report), Trial Steering Committee, investigators or collaborators.

9.5 Analysis Plan

The trial will be analysed and reported following the 'Consolidated Standards of Reporting Trials (CONSORT)' guidelines.

All statistical analyses will be on an intention to treat basis. Missing data, which are anticipated to mainly affect the quality of life outcome measure, will be handled by considering the robustness of the complete case analysis to sensitivity analyses using different imputation assumptions informed by data collected on reasons for missing data. Continuous variables will be summarised by descriptive statistics (mean, standard deviation, minimum, median and maximum) and frequency tables will be provided for categorical data.

Proportions of patients relapsing, under the various primary and secondary outcomes will be estimated together with 90% confidence intervals. RFS, PFS, OS, EFS will be estimated by the method of Kaplan and Meier. Cumulative incidence analysis adjusting for the competing risk of death/progression to BC will be used to estimate the cumulative incidence function of TTR.

Quality of life measurements will be assessed over time and comparisons made between relapsing and non-relapsing patients, using longitudinal analysis with appropriate recognition for informative dropout.

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- Results in death.
- Is life-threatening* (subject at immediate risk of death).
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**.
- Results in persistent or significant disability or incapacity.
- Consists of a congenital anomaly or birth defect.
- Observations of 'Blasts', Blast crisis', 'Acute leukaemia' or 'Transformation'.
- Other important medical events***.

*Life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Notes on Serious Adverse Event Inclusions and Exclusions

10.1.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsen following the de-escalation of the trial/trial treatment
- Laboratory anomalies that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

10.1.2 Do Not Include

- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before de-escalation of treatment that do not worsen

- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

10.1.3 Reporting of Pregnancy

If a patient or their partner becomes pregnant during trial treatment or within 28 days following treatment, a completed Pregnancy Report Form must be faxed to the LCTU within 24 hours of learning of its occurrence. (Should you need a copy of the Pregnancy Report Form please contact the Trial Coordinator). On pregnancy outcome, the final Pregnancy Report Form should be faxed to the LCTU 28 days after the outcome. The final Pregnancy Report Form is used to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up information on this form also includes an assessment of the possible relationship to the trial medication of any pregnancy outcome. Pregnancy outcomes should also be collected for the female partners of male patients participating in the trial. Consent to report information regarding these pregnancy outcomes should be obtained from the mother prior to completion and faxing of the final Pregnancy Report Form. Any SAE experienced during pregnancy must be reported on the SAE form.

The LCTU will report all pregnancies to the trial Sponsor(s), MHRA and MREC.

Pregnancies must be reported by faxing a completed Pregnancy Report Form sent within 24 hours of becoming aware of the event to the Liverpool Cancer Trials Unit
Fax. No. 0151 794 8931

Pregnancy outcomes must be reported by faxing a completed final Pregnancy Report Form 28 days following the outcome to the Liverpool Cancer Trials Unit
Fax No. 0151 794 8931

10.2 Notes Severity / Grading of Serious Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant. Severity of any SAE will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.

The SAE severity must be assessed according to medical criteria alone using the values in CTCAE or, should the SAE not be listed, by following corresponding categories:

Grade 1 (Mild): does not interfere with routine activities
Grade 2 (Moderate): interferes with routine activities

Grade 3 (Severe): impossible to perform routine activities
Grade 4 (Life threatening)
Grade 5 (Death)

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE does not need reporting, whereas a serious AE would be reportable as a Serious Adverse Event.

10.3 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 4.

If any doubt about the causality exists the local investigator should inform the trial coordination centre who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 4: Definitions of Causality

Relationship	Description
None	There is no evidence of any causal relationship. N.B. An alternative cause for the SAE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.4 Expectedness

An SAE whose causal relationship to the trial drug is assessed by the investigator as "possible", "probable", or "highly probable" is an Adverse Drug Reaction.

All events judged by the investigator to be possibly, probably, or highly probably related to the IMP, graded as serious and **unexpected** for list of Expected Adverse Events (see Reference Safely Information section 10.6) should be reported as a SUSAR.

10.5 Reference Safety Information

The Reference Safety Information (RSI) to be used for this trial is as follows:

GLIVEC film coated tablets – Summary of Product Characteristics – imatinib mesilate – Section 4.8

TASIGNIA 200mg hard capsules – Summary of Product Characteristic – nilotinib hydrochloride monohydrate – Section 4.8

SPRYCEL 20mg 50mg 80mg 100mg and 140mg film coated tablets – Summary of Product Characteristics – dasatinib monohydrate – Section 4.8

10.6 Follow-up After Serious Adverse Events

All SAEs should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.7 Reporting Procedures

All SAEs should be reported from the date of informed consent until 28 days after the last dose of treatment received in the de-escalation phase (or longer if felt to be a long-term side effect of trial treatment). Any questions concerning SAE reporting should be directed to the LCTU in the first instance.

10.7.1 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported within 24 hours of the local site becoming aware of the event by faxing an SAE form to the Liverpool Cancer Trials Unit on 0151 795 8931. This form is downloadable from the CRF section of the DESTINY eTMF here http://www.lctu.org.uk. If this website is also unavailable the site should contact the DESTINY Trial team on 0151 795 5479 and a copy of the form can either be emailed or faxed as required. In the unlikely event that all electronic systems are unavailable the SAE can be reported verbally and documentation completed when it later becomes available.

The person reporting the event should also phone the Trial Co-ordinator on 0151 795 5479 to alert that an SAE is being reported. On reporting an SAE to the LCTU, research sites will receive an acknowledgement. This will either be in as an email or a fax. If a receipt has not been received within two hours of submitting the SAE please ring the Trial Co-Ordinator for confirmation.

The completed SAE form should be assessed and each page signed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' that is responsible for the patient's care. The investigator should assess the SAE for the likelihood that that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team. The responsible investigator should check the SAE form, make changes as appropriate and sign as soon as possible. The initial report shall be followed by detailed, written reports.

i. The responsible investigator must **notify** their R&D department of the event (as per standard local procedure).

ii. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
iii. **Follow-up information is noted on the same SAE form.** Extra, annotated information and/or copies of test results may be provided separately.
iv. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

The Investigator must institute appropriate therapeutic action and follow-up measures in accordance with Good Medical Practice and should notify the trial co-ordinator of such actions.

Follow-up information should be provided within 5 days if the reaction/event had not resolved at the time of initial reporting.

The minimum dataset required for a preliminary report should include the following.

Page 1

- Patient trial number and initials.
- Days since last dose of trial treatment
- Date of onset of event.
- Outcome (i.e. current status).
- Overall diagnosis of event, with CTCAE grade.
- Relevant medical history or concurrent medical conditions

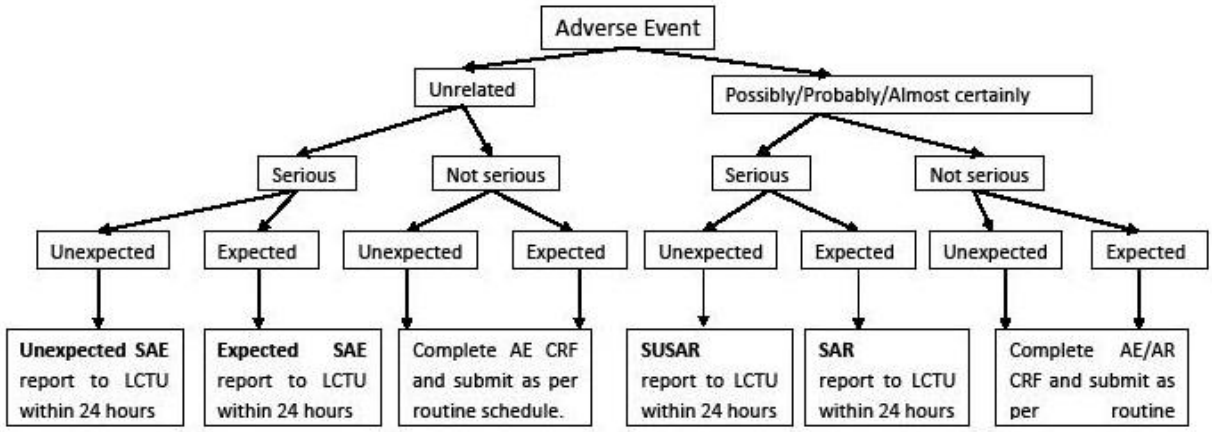
Page 2

- Any changes in drug treatment
- Serious criteria
- Causality (investigator completes)

Page 3 onwards

- Trial Medication and concurrent drug information, including causalities

The LCTU will notify the MHRA, MREC and co-sponsors of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the trial. Local investigators should report any SUSARs and/or SAEs as required by their Local Research Ethics Committee and/or Research & and Development Office.



10.8 Responsibilities – CR:UK LCTU

The LCTU is undertaking duties delegated by the trial co-sponsor/s, Royal Liverpool & Broadgreen University Hospital NHS Trust and the University of Liverpool, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the LCTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the LCTU first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-trial SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal trial (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the LCTU will liaise with the designated Clinical Co-ordinator who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified

and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The LCTU will also send an annual safety report containing a list of all SARs (including SUSARs) to the regulatory authorities.

From September 2011 the sponsor will submit a Development Safety Update Report (DSUR).

The DSUR will present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period relating to the Investigational Medicinal Product it will cover the following 4 areas:

(1) Examine whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety
(2) Describe new safety issues that could have an impact on the protection of clinical trial subjects
(3) A summary of the current understanding and management of identified and potential risks
(4) Provide an update on the status of the clinical investigation/development programme and trial results.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The trial will be conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments (Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

The trial will be conducted in accordance with the EU Directive 2001/20/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 and the principles of Good Clinical Practice.

Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

This trial may be terminated at the request of the Chief Investigator, Independent Safety and Data Monitoring Committee, Independent Ethics Committee or the MHRA if, during the course of the trial, concerns about the safety of further dosing emerge.

The Chief Investigator will update the ethics committee of any new information related to the trial drug when appropriate.

11.2 Ethical Approval

The trial protocol has received the favourable opinion of the Multi-centre Research Ethics Committee (MREC) but must undergo site specific assessment (SSA) by completing section C of the REC application form and submitting all sections of this form to the NHS R&D offices). A copy of local Research & Development (R&D) approval and of the PIS and CF on local Trust headed paper should be forwarded to LCTU before patients are entered.

Consent should be obtained prior to each patient participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. The right of patients to refuse their consent to participate in the trial without giving reasons must be respected.

After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in LCTU coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. Appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research trial to the patient and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided.

After being given adequate time to consider the information, the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient representative for their records and a copy placed in the medical records, with the original retained in the Investigator Site File.

The patient may withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this trial.

11.4 Trial Discontinuation

The reason for discontinuation of trial treatment/trial should be clearly documented and the End of Trial Treatment form completed.

12 REGULATORY APPROVAL

This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is its EudraCT number: 2012-004025-24. .

13 TRIAL MONITORING

13.1 Risk Assessment

In accordance with the LCTU Standard Operating Procedure a risk assessment has been completed in partnership with:

- Representatives of the Trial Sponsors (University of Liverpool and Royal Liverpool and Broadgreen University Hospital NHS Trust)
- Chief Investigator
- Trial Coordinator
- Trial Statistician
- LCTU Operational Director

In conducting this risk assessment, the contributors considered potential patient, organisational and trial hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment is assigned according to the following categories:

- Type A: no higher than that of standard medical care
- Type B: somewhat higher than that of standard medical care
- Type C: markedly higher than that of standard medical care

Following risk assessment this trial is considered to be Type A.

13.2 Source Documents

Source Data

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).

Source Documents

Original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial (ICH E6, 1.52).

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. Data recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses' notes). Each participating site should maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

For data where no prior record exists and which are recorded directly in the CRF (e.g. inclusion/exclusion criteria, adverse events and Quality of life questionnaires), the CRF will be considered the **source document,** unless otherwise indicated by the investigator.

In addition to the above, date(s) of conducting informed consent including date of provision of patient information, registration number, trial treatment and the fact that the patient is participating in a clinical trial should be added to the patient's medical record contemporaneously.

13.3 Data Capture Methods

Trial data will be captured using paper case report forms (CRFs).

13.3.1 Case Report Forms

The trial CRF is the primary data collection instrument for the trial. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

CRFs will be available for download from the LCTU website http://www.lctu.org.uk. To ensure current versions of CRFs are used, please print pages directly from the LCTU website as and when they are needed.

13.4 Monitoring at LCTU

13.4.1 Green Light Process

The Green Light Process in place at the LCTU means that no patients can be registered at a particular site without the green light having been given. It ensures that all approvals must be in place, all contracts/agreements signed and all trial-specific and ICH GCP training received by site research staff before patients can enter the trial.

13.4.2 Site Research Staff

All site research staff involved in the trial must be included on the delegation log. The PI at each site signs off on the delegation log only those staff members he/she feels are able and competent to complete the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities, and is continuously checked (as part of the data management plan) against staff named on CRFs, SAE reports and registration forms.

The TC ensures that as a minimum the PI, a research nurse, and a member of pharmacy staff at site have trial-specific training (on the protocol, SAE reporting and consent process) all of which is provided at site initiation (either on site or by teleconference) by the TC. The PI is responsible for ensuring site staff named on the

delegation log but not present at site initiation receive trial-specific training (on the protocol, SAE reporting and consent process). Sites are supplied with copies of training aids presented at site initiation to provide a constant reminder of key trial issues. Delegated site research staff must also submit their CV and provide the date of their last ICH GCP training. In order to ensure that site research staff maintain up to date ICH GCP training (to be renewed every 2 years as suggested by ICH GCP), an automated email reminder is sent to site research staff when their next ICH GCP training is due. Non-NHS staff must have honorary NHS contracts.

Automated 6-monthly email reminders (from site opening) are sent to sites requesting that an updated delegation log is faxed to LCTU. On receipt of updated delegation logs, the TC ensures that new staff members have submitted their CVs and date of last ICH GCP training.

13.4.3 Oversight Committees

The ISDMC is an independent multidisciplinary group that, collectively, have experience in haematological oncology and in the conduct of clinical trials. It is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial and for monitoring the overall progress and conduct of the clinical trial. See section 16 for further details.

The TSC includes an independent Chairman and others, plus members of the Trial Management Group (TMG). Among other things, the TSC takes responsibility for monitoring and supervising the progress of the trial, considering recommendations from the ISDMC and advising the TMG on all aspects of the trial. See section 16 for further details.

13.4.4 Safety Reports

Monthly safety reports are generated by the TC which allows monitoring of SAE reporting rates across sites. The ISDMC also regularly review adverse event reporting, and the TC prepares Annual Safety Reports for submission to the MHRA and research ethics committee. Any concerns raised by the ISDMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the TC to carry out site visits if there is suspicion of unreported SAEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines (as outlined in the pharmacovigilance plan) is noted at a given site.

13.4.5 Registration

The TC verifies that all site research staff attended trial-specific training relating to eligibility screening and the informed consent, and registration processes. Prior to registration, the TC/data manager (DM) carry out a check of all consent forms sent to the LCTU. This includes checking that the patient is eligible, the correct versions of the PIS and Patient Informed Consent (PIC) forms have been used and the patient and clinician signatures are present and dated on the same day.

When registering a new patient, the computerised program used for registration protects against errors by its inbuilt validation checks on site green light status, patient eligibility and informed consent. The trial statistician checks at intervals over the course of the recruitment period to confirm that the registration dates of consecutive registration numbers are in the correct order and that there are no missing registrations. The dates and outcome of these checks are specified on the registration checklist form to coincide with ISDMC meetings.

LCTU staff members receive appropriate registration training and there is always office cover to ensure the registration procedures are carried out correctly. The TC maintains a record of registration errors and notifies the trial statistician as they occur. Registration problems are monitored by the ISDMC, and if it is noted that a particular site is making consistent errors in the consent or registration processes, additional training will be provided by the TC to rectify the problem.

13.4.6 Patient Confidentiality

All LCTU and site research staff members have received ICH GCP training and are thus aware of the importance of patient confidentiality. The TC/DM consistently check that the CRFs sent to LCTU are all anonymised and are identifiable only by registration number (except for signed consent forms, which are stored in a locked cabinet in the LCTU). The TC will monitor site performance on maintaining patient confidentiality and will provide additional training if a particular site sends any patient identifiers to LCTU (other than on the signed consent form).

13.4.7 Recruitment

The TC will produce monthly recruitment reports, to allow the ISDMC, TSC and TMG to regularly review recruitment across sites. Slow or inconsistent recruitment will trigger further action centrally. The TC may liaise directly with site staff in order to query reasons for slow recruitment and try to resolve any problems that could impact recruitment. The TC will check that the trial is being actively promoted at sites, and site recruitment schedules will be reviewed during the course of the trial as necessary.

13.4.8 Protocol violations/deviations

All protocol violations and deviations are recorded by the TC in the trial site status database, and are included in the regular ISDMC reports. The TC sends details of all protocol violations and deviations to the CI as soon as the LCTU is made aware of such occurrences, and any that are considered to be a potential serious breach would be forwarded immediately to the Co-sponsors. If it is noted that a particular site is making consistent protocol violations or deviations, additional training will be provided by the TC.

13.4.9 Withdrawals, losses to follow up and missing data

The TC will produce reports on withdrawals, losses to follow-up and the quantity of missing CRFs/data across sites for review by the LCTU business meeting, TMG, TSC

and ISDMC. Identified problems will be discussed and remedial action taken as necessary.

As outlined in the data management plan, the TC/DM will check that the withdrawal CRF is completed for all withdrawn patients (including the reasons for withdrawal). The TC will compare withdrawal rates and reasons for withdrawal across centres, paying particular attention to withdrawals close to dates of registration. If a certain site experiences an excessive rate of withdrawals, additional training on the informed consent procedure will be provided.

13.4.10 Data management plan

CRF data entered into the MACRO database will be centrally monitored by the LCTU to ensure that data collected are consistent with adherence to the trial protocol. The MACRO database used for this trial includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query is raised within the MACRO database and emailed to site. A complete log of discrepancies and data amendments is automatically generated by MACRO, including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail. Automated email reminders are generated by the database if follow up data from a scheduled patient visit is overdue.

Additional site training will be carried out if recurring problems are noted with data from a certain site, such as consistently incorrect or incomplete data, a backlog of unresolved queries, or unacceptable time delays in submitting CRFs.

13.4.11 LCTU staff

All LCTU staff will receive regular ICH GCP training, have in-house training records and undergo regular Individual Performance Review (IPR) sessions, all of which are used to ensure that appropriate training is received and any problems identified and resolved in a timely fashion.

13.5 Clinical Site Monitoring

13.5.1 Direct access to data

Site monitoring may be deemed to be necessary as a result of central data checks. In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Each PI therefore permits trial related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents. As this also affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form

13.5.2 Confidentiality

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited. Case report forms will be labelled with patient initials and unique trial registration number. Samples will be transferred to the Universities of Glasgow and Imperial College London, Hammersmith

Hospital, and will be identifiable by unique trial registration number only. Consent forms sent to the LCTU as part of the registration process may contain patient identifiers for the purpose of monitoring as described in the trial risk assessment. Such information will be stored within the patient folders in secure, locked cabinets.

13.5.3 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The DESTINY Investigational sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent authorities or IEC. Such audits/inspections may take place at any site where trial related activity is taking place (the Sponsor's site(s), the LCTU or at any investigator's site including laboratories, pharmacies etc.)

The site staff should assist in all aspects of audit/inspection and be fully cognisant of the LCTU communication strategy for multicentre trials. This includes management systems for the green light process prior to site opening, conforming to the total Quality Management System currently operating within the LCTU.

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until the LCTU informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTU undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the LCTU by recruiting centres. This requires that name data will be transferred to the LCTU, which

is explained in the PISC. The LCTU will preserve the confidentiality of participants taking part in the trial and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

14 INDEMNITY

DESTINY is jointly sponsored by The Royal Liverpool & Broadgreen University Hospital NHS Trust and the University of Liverpool, and will be co-ordinated by the LCTU in the University of Liverpool. The Royal Liverpool & Broadgreen University Hospital NHS Trust and the University of Liverpool do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated trial, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability: NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven. The Royal Liverpool & Broadgreen University Hospital NHS Trust and the University of Liverpool does not accept liability for any breach in any other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

15 FINANCIAL ARRANGEMENTS

This is a non-commercial trial, and no direct payments are available to cover the costs associated with patient recruitment, treatment administration, follow-up visits, data collection or travel expenses. The trial has been funded and approved by the Leukaemia and Lymphoma Research Clinical Trials Committee and is therefore automatically adopted by the National Cancer Research Network (NCRN) and UK Clinical Research Network (UKCRN). These organisations will be responsible for providing local investigators with the necessary research infrastructure

16 TRIAL OVERSIGHT COMMITTEES

16.1 Trial Management Group (TMG)

The Trial Management Group (TMG) comprises the Chief Investigator, Co-Investigators, Health Economist, Trial Statistician and the LCTU trial team; as well as representatives from both of the Co-Sponsors and LCTU Operational Director.

The TMG will be responsible for the day-to-day running and management of the trial and will meet at least three times per year.

16.2 Trial Steering Committee (TSC)

The composition of the TSC is as follows. Membership details are available from the Trial Coordinator.

Chairman
Chief Investigator
Research Nurse with CML experience
Consultant Haematologist (current or retired) with CML experience x 3
Statistician
Patient representatives x 2
Trial Statistician
Trial Coordinator

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The composition of the ISDMC is as follows. Membership details are available from the Trial Coordinator.

Chairman
Statistician
Clinician

The Chief Investigator, Trial Statistician and Trial Co-ordinator will also be invited to attend ISDMC meetings.

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC will define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 9.

The ISDMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the trial.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and the named authors should include the trial's Chief Investigator, Statistician(s) and Trial Manager(s) involved. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

18.1 Version 1 (21 March 2013)

Original Approved version.

18.2 Version 2 (03 February 2014)

Changes from protocol version 1

Main changes

Inclusion Criteria (sections 1 & 5)

- Clarification that reporting of molecular results should be to International Standard where possible. This clarification is also reflected throughout the protocol.
- Clarification that potential patients without a standard BCR-ABL1 fusion transcript only *may be* eligible to participate.

Exclusion Criteria (sections 1 & 5)

- The criterion that excludes patients with previous higher than standard dose has been modified to include an exception to allow higher dose patients that participated in specific studies to be included as they do not demonstrate resistant disease.
- Clarification that patients who are already being treated with lower doses for tolerance reasons are allowed, providing their current dosage it at least 50% of the defined standard dose.
- Running order of exclusion criteria changed as result of the changes to allow a better reading 'flow'.

Overall Design (section 4.1)

- Clarification that samples should continue to be collected for relapsed patients until the molecular result at study entry is regained.

Primary Endpoint (section 4.2)

- Rewording for clarity of the primary endpoint.
- The line on there being no routine marrow examinations removed.

Samples (section 6.3)

- This section has been updated so only patients recruited and treated at the Royal Liverpool Hospital are requested to provide blood samples for sending to the Liverpool labs. This is also reflected throughout the protocol.
- Sample collection time-points clarified and receptacles to be used, plus kits that are provided have been updated; contact details for the labs have also been added.
- Additional samples from diagnostic blood tests being sent to Hammersmith has been updated to include all patients, rather than just those from the MR4 group, and clarified in the samples table.

Accountability Procedures for Trial Treatment (section 7.2)

- This section has been re-written to confirm that the Trial is a 'Type A' and that no accountability is required.
- Confirmation that other treatment supply practices (e.g. community pharmacy, homecare provider) are allowed if the PI approves.

Schedule of Trial Procedures (section 8.1)

- Updated so procedures are indicated by individual month, rather than grouping months together.
- Confirmation that 'after relapse' procedures only need to be undertaken until molecular status at original trial entry is restored.
- Inclusion of the previously omitted combined patient drug diary and disease symptom record (see section 8.2.3 also).

Planned assessments during 'stopping' follow-up phase (13-37 months) (section 8.1.4)

- Post month 37 PCR results (i.e. local) also being required has been added to this section.

Trial closure (section 8.7)

- Confirmation that enrolment to each molecular group will cease when its required number is reached added.

Pharmacovigilance (section 10)

- Confirmation that CTCAE v4 is being used to grade SAEs and advice provided on how to grade should the event not be listed in said version.
- Elaboration on the difference between severe and serious events added.
- Location of downloadable SAE forms in case of database unavailability clarified (section 10.2).
- Minimum dataset for preliminary report updated (section 10.7.1).

Minor/administrative changes

- Clarification that the patient diary will also be used to collect information on patients' symptoms (section 7.3).
- Time-points on when screening and baseline assessments need to be performed have been added (sections 8.1.1 & 8.1.2).
- Composition of oversight committees deleted from section 13.4.3 as it's covered in section 16
- References to 'start of treatment' (or similar) replaced with 'commencement of de-escalation' (or similar).
- Clarification that eligibility procedures need to be completed within certain timeframes of the commencement of de-escalation and not entry to the trial.
- Terminology for an extra blood test to confirm molecular relapse changed to 'Hammersmith Alert'.
- Number of sites increased.
- Other miscellaneous admin changes

18.3 Version 3 (18 December 2014)

Changes from protocol version 2

Main changes

Molecular Grouping

- Deletion of statement 'Enrolment to each molecular group will cease once the required number of patients for that particular group has been reached.' Deleted from section 8.7.
- Reference to 2 equal groups of 84 MMR and MR4 patients removed throughout and replaced with 1 group of 168 MMR and MR4.

18.4 Version 4 (16 January 2015)

Changes from protocol version 3

Main changes

Throughout

- Clarification that the central analysis definition of MMR is a BCR-ABL1/ABL1 ratio of ≤0.1% to International Standards (IS)
- Clarification that samples should continue to be collected for relapsed patients until MMR is regained

Contact details

- Addition of extra medical expert who will assess SAE reports

Protocol summary (section 1)

- Exclusion criterion 9 expanded to cover prior use of interferon
- 'Objectives' renamed 'Outcomes' and the secondary outcomes expanded

Overall design (section 4.1)

- Clarification that the study is a phase IIb

Secondary endpoints (section 4.3)

- List expanded

Trial population (section 5)

- Duplicated inclusion and exclusion criteria replaced with instruction to refer to the same in the protocol summary. Section numbering altered as a result.

Enrolment/Baseline (section 6.2)

- Updated to allow emailed registrations.

Samples required (section 6.3.1)

- Quantity of marrow tissue required updated to 1-2ml in table 1 to be consistent with rest of section

- Clarification that month 37 or relapse marrow samples should still be requested even if a baseline one wasn't available, and that the quantity of marrow should be taken according to local practice

Accountability procedures for Trial Treatment (section 7.2)

- Section re-worded for clarity and reference to 'Type A' trial removed as this is covered in the risk assessment section of the protocol.

Assessments and procedures (section 8)

- Clarified throughout that molecular monitoring is reported to international standards and not just where possible, and that samples should continue to be collected for relapsed patients until MMR is regained

Schedule of trial procedures (section 8.1)

- Table 3 updated to include Hammersmith alert procedures and weight measurement requirement at all post screening visits
- Baseline marrow window extended to 1 calendar month prior to the commencement of de-escalation
- Table legend updated accordingly

Planned assessment at relapse (section 8.1.5)

- Addition to clarify that baseline samples are not included in the establishing of relapse

Statistical introduction (section 9.1)

- Updated to include the reclassification of MR4 patients for statistical analysis purposes, plus rationale of same

Secondary endpoints (section 9.2.2)

- Secondary endpoints expanded and confirmation that they will be calculated separately for each molecular group added

Sample size (section 9.3)

- Section completely updated to reflect the changes to the molecular grouping

Interim monitoring analyses (section 9.4)

- Triggers for interim analyses updated and addition that such results are confidential to ISDMC members only

Analysis plan (section 9.5)

- Reporting to 'CONSORT' guidelines added
- Use of Kaplan and Meier and cumulative incidence analysis methods for stipulated estimations added

Pharmacovigilance (section 10)

- Definitions of SAE expanded
- Erroneous use of grading to WHO toxicity criteria removed
- Online reporting instructions replaced with those for paper reporting

Risk assessment (section 13.1)

- Low/moderate/high risk categories replaced with Type A/B/C.

Minor/administrative changes

Throughout

- Updates to contact details and grammatical errors

18.5 Version 5 (04 July 2016)

Changes from Protocol V4

Protocol summary (section 1)

- Update to diagram (wording)

Overall design (section 4.1)

- Change to wording in Paragraph 4

Schedule of trial procedures (section 8.1)

- Table 3 updated to include Relapse procedures

18.6 Version 6 (22 March 2017)

Changes from Protocol V5

Protocol summary (section 1)

- Update to diagram (spelling)

Schedule of trial Procedures (section 8.1)

- Removal of requirement for Bone Marrow at Month 37
- Removal of 30mls blood for Liverpool patients at Month 37
- Addition of follow up for patients after Month 37

Update to Reference Safety Information (section 10.5)

- Correction to references to Reference Safety Information

18.7 Version 7 (24 May 2018)

Changes from protocol V6

Removal of secondary end point:
Proportion of patients who develop a BCR-ABL1 kinase domain mutation at a level of >20% of all BCR-ABL1 transcripts on at least 2 consecutive occasions

Contact details:
Update to study statistician

Updates to Trial Treatment (Section 7)

Updated references to SmPCs. Clarified processes for non-protocol dosing. Removed wording relating to licenced indication, dosage and form. Confirmed method of dose reduction.

19 REFERENCES

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