Clinical trial results:
A trial of de-escalation and stopping treatment in chronic myeloid leukaemia patients with excellent responses to tyrosine kinase inhibitor therapy DESTINY(De- Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in chronic myeloid leukaemia)

Summary

EudraCT number	2012-004025-24
Trial protocol	GB
Global end of trial date	01 August 2018

Results information

Result version number	v1 (current)
This version publication date	06 October 2019
First version publication date	06 October 2019

Trial information

Trial identification

Sponsor protocol code	4203/UoL000893

Additional study identifiers

ISRCTN number	ISRCTN74084226
ClinicalTrials.gov id (NCT number)	NCT01804985
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Royal Liverpool and Broadgreen University Hospitals NHS Trust
Sponsor organisation address	Prescot Street, Liverpool, United Kingdom, L7 8XP
Public contact	RD&I research Governance Manager, The Royal Liverpool and Broadgreen University Hospitals NHS Trust, 0151 7063320, lucy.read@liverpool.ac.uk
Scientific contact	RD&I research Governance Manager, The Royal Liverpool and Broadgreen University Hospitals NHS Trust, 0151 7063320, lucy.read@liverpool.ac.uk
Sponsor organisation name	University of Liverpool
Sponsor organisation address	2nd Floor Block D Waterhouse Building, Liverpool, United Kingdom, L69 3GA
Public contact	Research Support Manager, University of Liverpool, 0151 7948739, Sponsor@liverpool.ac.uk
Scientific contact	Research Support Manager, University of Liverpool, 0151 7948739, Sponsor@liverpool.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary endpoint of the study is the proportion of patients who lose MMR during the trial observation period of 37 months. BCR-ABL1 will be assessed by standard PCR based molecular monitoring on blood. This is a routine part of clinical follow-up, but will be carried out more frequently than usual. It is not expected that any patient will undergo more serious relapse than loss of MMR, so there are no formal plans for routine marrow examinations. MR4 and MMR patients will receive the same strategy, but will be analysed separately.

Protection of trial subjects:

The study involved a de-escalation of patient's prescribed medication for CLL, followed by stopping of their medication. As part of analysis, and as a continuous indication of patient health, monthly bloods were taken and analysed for relapse.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 174
Worldwide total number of subjects	174
EEA total number of subjects	174

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	111
From 65 to 84 years	62
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial opened to recruitment in December 2013 and closed in April 2015. Although the target number of patients was 168, 174 patients were enrolled in the study. This was due to ethical reasons as patients at different sites were still in the process of joining when the trial was approaching recruitment termination.

Pre-assignment

Screening details:

A total of 336 patients were screened for the trial. Main reasons for decline included the commitment to monthly visits, the additional bone marrow test and reduction/cessation of treatment dose. Main reasons for exclusion included inadequate PCR lab results and higher or lower TKI doses than required.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	De-escalation
Arm description: -	
Arm type	De-escalation
Investigational medicinal product name	Imatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 200mg once daily	
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 200mg twice daily	
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 50mg once daily	

Number of subjects in period 1	De-escalation
Started	174
Completed	174

Period 2	
Period 2 title	De-escalation
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	De-escalation
Arm description: -	
Arm type	De-escalation
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	De-escalation
Started	174
Completed	159
Not completed	15
Relapse	10
Study drop-out	5

Period 3	
Period 3 title	Cessation
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	De-escalation
Arm description: -	
Arm type	De-escalation
No investigational medicinal product assigned in this arm	

Number of subjects in period 3[1]	De-escalation
Started	153
12 month cessation	103
Completed	94
Not completed	59
Relapse	54
Study drop-out	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 4There were 6 patients (4 MMR and 2 MR4) that completed 12 months of de-escalation although they did not start cessation phase. The summaries in brackets refer to those patients.

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Baseline patients are summarised for the full cohort of 174 recruited patients.	

Reporting group values	Baseline	Total	
Number of subjects	174	174	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age was calculated as the years between date of birth and date of recruitment.			
Units: years			
arithmetic mean	57.6		
standard deviation	± 13.4	-	
Gender categorical Units: Subjects			
Female	76	76	
Male	98	98	
ECOG Performance Status Units: Subjects			
Ambulatory (work able)	17	17	
Ambulatory (Not Work Able)	1	1	
Fully Active	155	155	
Limited Self Care	1	1	
CML Medication Units: Subjects			
Dasatinib	10	10	
Imatinib	148	148	
Nilotinib	16	16	
Weight Units: kg			
arithmetic mean	82.2		
standard deviation	± 16.0	-	
WBC Units: x 10^9			
arithmetic mean	6.0		

standard deviation	± 1.9	-	

Subject analysis sets	
Subject analysis set title	MMR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

At least 3 molecular results over the preceding 12 months of registration, each with at least 10000 ABL1 control transcripts and BCR-ABL/ABL1 ratio of below or equal 0.1% (but above 0.01%).

Subject analysis set title	MR4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

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.

Reporting group values	MMR	MR4	
Number of subjects	53	121	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age was calculated as the years between date of birth and date of recruitment.			
Units: years arithmetic mean standard deviation	 53.6 ± 14.3	 59.4 ± 12.6	
Gender categorical Units: Subjects			
Female Male	26 27	50 71	
ECOG Performance Status Units: Subjects			
Ambulatory (work able) Ambulatory (Not Work Able) Fully Active Limited Self Care	7 0 46 0	10 1 109 1	
CML Medication Units: Subjects			
Dasatinib Imatinib	5 45	5 103	

Nilotinib	3	13	

Weight			
Units: kg			
arithmetic mean	79.6	83.3	
standard deviation	± 15.5	± 16.1	
WBC			
Units: x 10^9			
arithmetic mean	5.7	6.1	
standard deviation	± 1.9	± 1.9	

End points

End points reporting groups

Reporting group title	De-escalation
Reporting group description: -	
Reporting group title	De-escalation
Reporting group description: -	
Reporting group title	De-escalation
Reporting group description: -	
Subject analysis set title	MMR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

At least 3 molecular results over the preceding 12 months of registration, each with at least 10000 ABL1 control transcripts and BCR-ABL/ABL1 ratio of below or equal 0.1% (but above 0.01%).

Subject analysis set title	MR4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

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.

Primary: Relapse rate

End point title	Relapse rate[1]

End point description:

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. Losses to follow-up and complete withdrawals (prior experiencing relapse) from the trial are excluded from the number of available patients for analysis.

End point type	Primary

End point timeframe:

Relapses are recorded from start of de-escalation phase until end of treatment cessation phase (3 years in total).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The website features do not allow the specify the primary endpoint analysis. No p-value was calculated but percentage estimate with 90% confidence interval, separately for the two subgroups.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	119[2]		
Units: subjects	15	79		

Notes:

[2] - Two patients withdrew consent.

Attachments (see zip file)	Primary Outcome.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse on cessation

End point title	Relapse on cessation

End point description:

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.

End point type	Secondary

End point timeframe:

Relapses occurred after the de-escalation phase within the treatment cessation phase (2 years in total).

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39[3]	114[4]		
Units: subjcts	22	32		

Notes:

[3] - These are the number of patients who completed de-escalation without relapsing.

[4] - These are the number of patients who completed de-escalation without relapsing.

Statistical analyses

No statistical analyses for this end point

Secondary: Regain of MMR

End point title	Regain of MMR

End point description:

Proportion of patients who lose their MMR on de-escalation/stopping and regain MMR on resumption of their TKI.

Information on MMR recovery was not available on two patients (MR4 group) as they were censored shortly after relapse.

End point type	Secondary

End point timeframe:

From point of relapse to regain of MMR or end of study.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[5]	36[6]		
Units: subjects	31	34		

Notes:

[5] - These is the number of patients who relapsed in MMR group.

[6] - These is the number of patients who relapsed in MR4 group.

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular-free survival

End point title	Molecular-free survival

End point description:

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).

For non-estimable values of median or lower/upper limit, the number zero has been used instead. The zeros and 10000000000 in the results below are not informative, please see attachment instead.

End point type	Secondary

End point timeframe:

From start of de-escalation until end of cessation phase (3 years).

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	121		
Units: months				
median (inter-quartile range (Q1-Q3))	16.12 (15.23 to 10000000000)	0 (0 to 10000000000)		

Attachments (see zip file)	Figure3_KMPlot_RelapseFreeSurvival.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

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)

Among the available data on progression, no disease progressions were experienced and only two patients died, both in MR4 group. One due to stenosis coronary atheroma and pulmonary heart disease with severe emphysema and the other because of ischaemic leg, after 35 and 3 months from starting de-escalation respectively. The number of events were too small and the analysis was not performed. The zeros in the value section are not informative.

End point type	Secondary

End point timeframe:

From start of de-escalation to end of cessation phase.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	121		
Units: months				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS); OS is defined as the time from the first day of de-escalation to the date of death from any cause.

Only two patients died, both in MR4 group. One due to stenosis coronary atheroma and pulmonary heart disease with severe emphysema and the other because of ischaemic leg, after 35 and 3 months from starting de-escalation respectively. The number of events were too small and the analysis was not performed. The zeros in the value section are not informative.

End point type	Secondary

End point timeframe:

From start of de-escalation phase to end of cessation phase.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	121		
Units: months				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival

End point title	Event-free survival

End point description:

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.

For non-estimable values of median or lower/upper limit, the number zero has been used instead. The zeros and 10000000000 in the results below are not informative, please see attachment instead.

End point type	Secondary

End point timeframe:

From start of de-escalation to end of cessation phase.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	121		
Units: months				
median (inter-quartile range (Q1-Q3))	16.12 (15.23 to 10000000000)	0 (0 to 10000000000)		

Attachments (see zip file)	Figure7_KMPlot_EventFreeSurvival.pdf

Statistical analyses

Statistical analysis title	Event-free survival

Statistical analysis description:

Estimates were calculated using Kaplan-Meier method. Median molecular-free survival estimate and 90% confidence intervals estimates are left blank where they were not estimable.

Comparison groups	MMR v MR4
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	≤ 0.001
Method	Chi-squared

Notes:

[7] - A formal test was performed to assess if there was any statistically significant difference between MMR and MR4.

Secondary: Time to MMR recovery

End point title	Time to MMR recovery

End point description:

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.

Information on MMR recovery was not available on two patients (MR4 group) as they were censored shortly after relapse.

End point type	Secondary

End point timeframe:

From relapse to restoration of MMR or end of study.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[8]	36[9]		
Units: months				
median (inter-quartile range (Q1-Q3))	2.37 (2.14 to 2.99)	2.15 (1.84 to 2.70)		

Notes:

[8] - These is the number of patients that relapsed in MMR group.

[9] - These is the number of patients that relapsed in MR4 group.

Attachments (see zip file)	Figure8_CumInc_MMR.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Mr4.5 prior study entry

End point title	Proportion of Mr4.5 prior study entry

End point description:

Proportion of MMR and MR4 patients in confirmed MR4.5 prior to entering the study.

Patients were evaluable for MR4.5 status if their most recent results prior entering the study showed at least 31,623 ABL1 control transcripts. Patients fulfilling this criteria with BCR-ABL ≤ 0.0032% IS were then considered as MR4.5 whereas patients fulfilling this criteria but with BCR-ABL > 0.0032% were considered as not MR4.5.

End point type	Secondary

End point timeframe:

Prior patients being registered in the study.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45[10]	105[11]		
Units: subjects	21	99		

Notes:

[10] - These are the number of patients evaluable.

[11] - These are the number of patients evaluable.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life - EQ index

End point title	Quality of life - EQ index

End point description:

EQ-index Score range: 0 – 100 (0: worst possible score, 100: best possible score)

Results were analysed over time not through a single estimate. The zeros in the results below are not informative, please see attachment instead.

End point type	Secondary

End point timeframe:

From baseline until end of cessation phase.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	117		
Units: score				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Attachments (see zip file)	Figure9_EQ_index.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - EQ VAS

End point title	Quality of Life - EQ VAS

End point description:

EQ-VAS Score range: 0 – 100 (0: worst possible score, 100: best possible score).

Results were analysed over time not through a single estimate. The zeros in the results below are not informative, please see attachment instead.

End point type	Secondary

End point timeframe:

From baseline until end of cessation phase.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	108		
Units: scores				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Attachments (see zip file)	Figure10_EQ_VAS.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - FACT-BRMTOI

End point title	Quality of Life - FACT-BRMTOI

End point description:

FACT-BRMTOI Score range: 0 – 106 (0: worst possible score, 106: best possible score)

Results were analysed over time not through a single estimate. The zeros in the results below are not informative, please see attachment instead.

End point type	Secondary

End point timeframe:

EQ-VAS Score range: 0 – 100 (0: worst possible score, 100: best possible score)

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	117		
Units: scores				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Attachments (see zip file)	Figure11_FACT_BRMTOI.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - FACT-G

End point title	Quality of Life - FACT-G

End point description:

FACT-G Score range: 0 – 106 (0: worst possible score, 106: best possible score)

Results were analysed over time not through a single estimate. The zeros in the results below are not informative, please see attachment instead.

End point type	Secondary

End point timeframe:

From baseline to end of cessation phase.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	116		
Units: scores				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Attachments (see zip file)	Figure12_FACT_G.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - FACT-BRM

End point title	Quality of Life - FACT-BRM

End point description:

FACT –BRM Total Score range: 0 – 160 (0: worst possible score, 160: best possible score)

Results were analysed over time not through a single estimate. The zeros in the results below are not informative, please see attachment instead.

End point type	Secondary

End point timeframe:

From baseline to end of cessation phase.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	114		
Units: scores				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Attachments (see zip file)	Figure13_FACT_BRM.pdf

Statistical analyses

No statistical analyses for this end point

Other pre-specified: TKI related symptoms

End point title	TKI related symptoms

End point description:

Data regarding TKI withdrawals-related symptoms.

Results were analysed over time not through a single estimate. The zeros in the results below are not informative, please see attachment instead.

End point type	Other pre-specified

End point timeframe:

From baseline to the end of cessation phase.

End point values	MMR	MR4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	121		
Units: subjects	0	0		

Attachments (see zip file)	Figure15_TKI_plot.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From the date of informed consent until 28 days after last dose of treatment received in the de-escalation phase (or longer if felt to be a long-term side effect of trial treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Safety set

Reporting group description:

All patients who received any trial treatment (started of de-escalation).
Non-serious adverse events were not recorded in this trial.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious adverse events were not recorded for this study.

Serious adverse events	Safety set		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 174 (9.77%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications - Other, specify	Additional description: Injury, poisoning and procedural complications - Other, specify: Injury - right shoulder, fall		
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Vascular disorders - Other, specify	Additional description: Vascular disorders - Other, specify: Anaphylaxis - patient admitted to Hight Dependency Unit with periorbital swelling, difficulty breathing and flushing (Grade 3)		
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain - cardiac			

subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	4 / 174 (2.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye disorders - Other, specify	Additional description: Eye disorders - Other, specify: Anaphylaxis (grade 3)		
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Gallbladder pain			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders - Other, specify	Additional description: Hepatobiliary disorders - Other, specify: Choledocholithiasis		
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorder - Other, specify	Additional description: Musculoskeletal and connective tissue disorder - Other, specify: Ruptured Achilles Tendon - Patient was doing keep fit and felt their left achilles tendon rupture. patient has been placed in an equinus walker boot with specific Achilles wedge.		
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 174 (1.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Skin infection			

subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 174 (1.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vaginal infection			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 174 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2014	• Clarification that reporting of molecular results should be to International Standard where possible and that potential patients without a standard BCR-ABL1 fusion transcript only may be eligible to participate. • 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'. • Clarification that samples should continue to be collected for relapsed patients until the molecular result at study entry is regained. • Rewording for clarity of the primary endpoint. • The line on there being no routine marrow examinations removed. • Sample 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. • Sample collection time-points clarified and receptacles to be used, plus kits that are provided have been updated • 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 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 are allowed if the PI approves. • Post month 37 PCR results (i.e. local) also being required has been added to this section • Confirmation that enrolment to each molecular group will cease when its required number is reached added.
18 December 2014	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.' • Reference to 2 equal groups of 84 MMR and MR4 patients removed throughout and replaced with 1 group of 168 MMR and MR4.

16 January 2015	• 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 • Addition of extra medical expert who will assess SAE reports • Exclusion criterion expanded to cover prior use of interferon • 'Objectives' renamed 'Outcomes' and the secondary outcomes expanded • Clarification that the study is a phase IIb • Duplicated inclusion and exclusion criteria replaced with instruction to refer to the same in the protocol summary. Section numbering altered as a result. • Updated to allow emailed registrations. • 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 • Section re-worded for clarity and reference to 'Type A' trial removed as this is covered in the risk assessment section of the protocol. • 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 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 • Addition to clarify that baseline samples are not included in the establishing of relapse • Updated to include the reclassification of MR4 patients for statistical analysis purposes, plus rationale of same. Update to sample size. • Update to analysis plan. • Clarification and expansion in pharmacovigilance section. • Risk assessment categories replaced.
04 July 2016	• Update to protocol summary diagram. • Changes to wording in overall design. • Schedule of procedure updated to include relapse procedures.
22 March 2017	• Update to diagram in protocol summary. • Removal of bone marrow and 30mls blood at month 37. Addition of follow-up patients after month 37. • Correction to references to Reference Safety Information.
28 May 2018	• Removal of one secondary endpoint. • Updated to contact details. • Updated references to SmPCs. Clarified processes for non-protocol dosing. Removed wording relating to licenced indication, dosage and form. Confirmed method of dose reduction.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported