Clinical trial results:
A randomised Phase II trial of Imatinib (IM) versus Hydroxychloroquine (HCQ) and Imatinib (IM) for patients with Chronic Myeloid Leukaemia (CML) in Cytogenetic Response (CyR) with residual disease detectable by quantitative polymerase chain reaction (Q-PCR)

Summary

EudraCT number	2009-014373-41
Trial protocol	GB DE FR
Global end of trial date	27 June 2017

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	H135

Additional study identifiers

ISRCTN number	ISRCTN61568166
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Ref Number: GN09HM575

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	Clinical Research and Development Central Office, Dykebar Hospital, Ward 11, Grahamston Road, Paisley, United Kingdom, PA2 7DE
Public contact	Dr Margaret Fegen, NHS Greater Glasgow and Clyde, 0141 314 4172, margaret.fegen@ggc.scot.nhs.uk
Scientific contact	Dr Margaret Fegen, NHS Greater Glasgow and Clyde, 0141 314 4172, margaret.fegen@ggc.scot.nhs.uk
Sponsor organisation name	University of Glasgow
Sponsor organisation address	University Avenue, Glasgow, United Kingdom, G12 8QQ
Public contact	Dr Debra Stuart, University of Glasgow, 0141 330 4539, debra.stuart@glasgow.ac.uk
Scientific contact	Dr Debra Stuart, University of Glasgow, 0141 330 4539, debra.stuart@glasgow.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

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	06 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2016
Global end of trial reached?	Yes
Global end of trial date	27 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To provide preliminary evidence that HCQ given in combination with imatinib is more effective than imatinib alone in terms of BCR/ABL levels in CML patients who are in major cytogenetic response with residual BCR/ABL+ cells after at least one year of imatinib treatment. • To determine the safety and tolerability of HCQ given in combination with imatinib in these patients.

Protection of trial subjects:

The role of the IDMC was to review the accruing trial data and to assess whether there were any safety or efficacy issues that should be brought to participants' attention or any reasons for the trial not to continue. The IDMC was independent the investigators and was the only body that had access to full accumulating data during the course of the trial. It made recommendations to the UTSC.

Background therapy: -

Evidence for comparator:

Imatinib treatment induces CCyR in the majority of CML patients, results in significantly improved survival and is currently front-line treatment for CML. However, most patients continue to have evidence of persistent residual disease detectable by quantitative polymerase chain reaction (Q-PCR) and there are several lines of evidence that residual BCR/ABL+ stem cells persist in CML patients despite Imatinib treatment. Therefore patients require to be treated with Imatinib indefinitely and remain at risk of relapse. Measures to enhance elimination of residual disease are needed to further improve outcomes and effect cure. In preclinical studies CML CD34+ cells were cultured for 6 days in the presence of Imatinib (IM), dasatinib (das), chloroquine (CQ) or combinations in serum free medium supplemented with growth factors prior to long term culture. Results show the recovery of CML stem cells, defined as LTCIC, confirming that combinations of IM or das with CQ are more effective in stem cell eradication than IM or das alone. We have therefore conclusively demonstrated that tyrosine kinase inhibitors, Imatinib, and dasatinib, induce the process of autophagy in CML stem and progenitor cells. In these cells autophagy acts as a survival process allowing the cells to generate energy and remain alive. Chloroquine and HCQ are well known inhibitors of autophagy that are used in laboratory studies, but can also be applied clinically. The combination of the autophagy inhibitor chloroquine with Imatinib results in significantly enhanced eradication of CML primitive progenitors compared to Imatinib or chloroquine alone. HCQ has been used extensively in rheumatology and is well tolerated. These results provide a strong rationale for testing whether addition of HCQ to Imatinib can enhance elimination of residual BCR/ABL+ stem/progenitor cells in Imatinib treated CML patients in MCyR.

Actual start date of recruitment	01 April 2010
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: 42
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	46
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Pre-randomisation evaluations:
• Inclusions/exclusions
• Vital signs
• Medical and CML history
• Physical examination
• ECOG PS
• 12 lead ECG
• Pregnancy test
• Visual acuity testing
• Haematology (FBC)
• Biochemistry (U+E, LFTs)
• Bone marrow aspirate for cytogenetics and PD
• Peripheral blood PD
• Peripheral blood Q-PCR

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Imatinib alone

Arm description:

Imatinib only.

Arm type	Active comparator
Investigational medicinal product name	Imatinib
Investigational medicinal product code	IM
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients will receive Imatinib at the dose they were taking prior to trial entry. Imatinib will be obtained from the same commercial source as was used prior to enrolment into the study. Patients should be instructed to take their oral dose of Imatinib at the same time each day. Daily treatment will be withheld only in the case of dose limiting toxicities. The prescribed dose should be administered orally, with a meal and a large glass of water. Patients should keep normal eating habits, however a low-fat meal is recommended avoiding xanthine (e.g. caffeine) or grapefruit containing foods or beverages. A minimum of 1h should be allowed between last drug intake and going to bed. If vomiting occurs, no additional Imatinib should be taken that day in an effort to replace the material that has been vomited. If the patient forgets to take his/her Imatinib dose on scheduled treatment days, then he/she should take it on that same day within 12 hours after the missed dose if possible.

Arm title	Imatinib plus Hydroxychloroquine

Arm description:

Imatinib and Hydroxychloroquine. Note that Hydroxychloroquine is only given for the first 12 months of treatment.

Arm type	Experimental

Investigational medicinal product name	Imatinib
Investigational medicinal product code	IM
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients will receive Imatinib at the dose they were taking prior to trial entry. Imatinib will be obtained from the same commercial source as was used prior to enrolment into the study. Patients should be instructed to take their oral dose of Imatinib at the same time each day. Daily treatment will be withheld only in the case of dose limiting toxicities. The prescribed dose should be administered orally, with a meal and a large glass of water. Patients should keep normal eating habits, however a low-fat meal is recommended avoiding xanthine (e.g. caffeine) or grapefruit containing foods or beverages. A minimum of 1h should be allowed between last drug intake and going to bed. If vomiting occurs, no additional Imatinib should be taken that day in an effort to replace the material that has been vomited. If the patient forgets to take his/her Imatinib dose on scheduled treatment days, then he/she should take it on that same day within 12 hours after the missed dose if possible.

Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	HCQ
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients will initially receive HCQ at 800mg/day. This will be taken as 400mg twice daily doses approximately 12 hours apart. Patients should be instructed to take their twice-a-day oral doses of HCQ at the same times each day (e.g. 8am and 8pm). Daily treatment will be withheld only in the case of dose limiting toxicities. The prescribed dose should be administered orally, with a meal or a glass of milk. A minimum of 1h should be allowed between last drug intake and going to bed. If the patient forgets to take his/her HCQ dose on scheduled treatment days, then he/she should take it on that same day within 6 hours after the missed dose if possible. After more than 6 hours, that dose should be withheld and the patient should wait to take HCQ at the next scheduled dose either that same day or the following day. Patients should be instructed not to try to make-up the missed dose after 6 hours. The patient should then continue treatment with the original dosing schedule.

Number of subjects in period 1	Imatinib alone	Imatinib plus Hydroxychloroquine
Started	30	32
Completed	30	32

Baseline characteristics

Reporting groups	
Reporting group title	Imatinib alone
Reporting group description:	
Imatinib only.	
Reporting group title	Imatinib plus Hydroxychloroquine
Reporting group description:	
Imatinib and Hydroxychloroquine. Note that Hydroxychloroquine is only given for the first 12 months of treatment.	

Reporting group values	Imatinib alone	Imatinib plus Hydroxychloroquine	Total
Number of subjects	30	32	62
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 at randomisation.			
Units: years			
median	50	50	
inter-quartile range (Q1-Q3)	42 to 66	39 to 61	-
Gender categorical Units: Subjects			
Female	10	9	19
Male	20	23	43
PCR level at study entry Units: Subjects			
< 3 logs below baseline	15	18	33
>= 3 logs below baseline	15	14	29
Time on Imatinib			
Time on Imatinib, at the time of randomisation.			
Units: Subjects			
< 24 months	4	6	10
24 to <36 months	5	5	10
>= 36 months	21	21	42
Current Imatinib dose			
Imatinib dose, at the time of randomisation.			
Units: Subjects			
< 400mg	2	1	3

400mg to <600mg	25	26	51
600 to 800mg	3	5	8
Centre			
Recruiting hospital.			
Units: Subjects			
BEATSON WEST OF SCOTLAND CANCER CENTRE GLASGOW	10	9	19
HAMMERSMITH HOSPITAL LONDON	5	6	11
HOSPICES CIVILS DE LYON LYON	9	9	18
NOTTINGHAM UNIVERSITY HOSPITAL NHS TRUST	2	3	5
ROYAL LIVERPOOL UNIVERSITY HOSPITAL LIVERPOOL	3	3	6
ST JAMES'S UNIVERSITY HOSPITAL LEEDS	1	0	1
UNIVERSITY HAMBURG HAMBURG	0	1	1
UNIVERSITY HOSPITAL AACHEN PAUWELSSTRASSE, AACHEN	0	1	1

End points

End points reporting groups

Reporting group title	Imatinib alone
Reporting group description:	
Imatinib only.	
Reporting group title	Imatinib plus Hydroxychloroquine
Reporting group description:	
Imatinib and Hydroxychloroquine. Note that Hydroxychloroquine is only given for the first 12 months of treatment.	
Subject analysis set title	Whole blood HCQ population
Subject analysis set type	Per protocol
Subject analysis set description:	
Based on the ITT population IM+HCQ arm, excluding the 6 IM + HCQ patients in the safety run-in period where blood samples were not taken. Patients who have not consented to blood sampling or have withdrawn consent have also been excluded.	
Subject analysis set title	Imatinib plasma population (IM only)
Subject analysis set type	Per protocol
Subject analysis set description:	
Based on the ITT population IM only arm, excluding the 6 IM only patients in the safety run-in period where blood samples were not taken. Patients who have not consented to blood sampling or have withdrawn consent have also been excluded.	
Subject analysis set title	Imatinib plasma population (IM+HCQ)
Subject analysis set type	Per protocol
Subject analysis set description:	
Based on the ITT population IM+HCQ arm, excluding the 6 IM+HCQ patients in the safety run-in period where blood samples were not taken. Patients who have not consented to blood sampling or have withdrawn consent have also been excluded.	

Primary: 12 month treatment success proportion

End point title	12 month treatment success proportion
End point description:	
The proportion of treatment “successes” defined as patients who have >0.5 log reductions in their 12 month PCR level from baseline. Patients who withdraw before the 12 month assessment or who have an increase in their IM dose prior to the assessment will be classified as treatment “failures”.	
End point type	Primary
End point timeframe:	
12 months post-randomisation	

End point values	Imatinib alone	Imatinib plus Hydroxychloroquine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percent				
Success	6	6		
Failure - did not achieve >0.5 log reduction	19	19		
Failure - increase in Imatinib dose	1	0		
Failure - withdrew consent prior to assessment	4	7		

Statistical analyses

Statistical analysis title	Primary efficacy analysis

Statistical analysis description:

The comparisons between the study arms of 12 month treatment "successes" rates will use Fisher's exact test. A 95% confidence interval for the difference in proportion will be calculated using method 10 in RG Newcombe.

Comparison groups	Imatinib alone v Imatinib plus Hydroxychloroquine
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.58 [2]
Method	Fisher exact
Parameter estimate	Difference in "success" proportions (%)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.1
upper limit	18.4

Notes:

[1] - 1-sided hypothesis test, set-up to show 12 month treatment "successes" rate is greater in the IM+HCQ arm than the IM alone arm.
[2] - 1-sided.

Secondary: 24 month treatment success proportion

End point title	24 month treatment success proportion

End point description:

The proportion of treatment "successes" defined as patients who have >0.5 log reductions in their 24 month PCR level from baseline. Patients who withdraw before the 24 month assessment or who have an increase in their IM dose prior to the assessment will be classified as treatment "failures".

End point type	Secondary

End point timeframe:

24 months post-randomisation

End point values	Imatinib alone	Imatinib plus Hydroxychloroquine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percent				
Success	5	12		
Failure - did not achieve >0.5 log reduction	19	13		
Failure - no 24 month BCR/ABL data	1	0		

Failure - increase in Imatinib dose	1	0		
Failure - withdrew consent prior to assessment	4	7		

Statistical analyses

Statistical analysis title	24 month treatment success proportion

Statistical analysis description:

The comparisons between the study arms of 24 month treatment "successes" rates will use Fisher's exact test. A 95% confidence interval for the difference in proportion will be calculated using method 10 in RG Newcombe.

Comparison groups	Imatinib alone v Imatinib plus Hydroxychloroquine
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.059 [4]
Method	Fisher exact
Parameter estimate	Difference in "success" proportions (%)
Point estimate	20.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	40.4

Notes:

[3] - 1-sided hypothesis test, set-up to show 24 month treatment "successes" rate is greater in the IM+HCQ arm than the IM alone arm.
[4] - 1-sided

Secondary: 12 month molecular response

End point title	12 month molecular response

End point description:

The proportion of patients who achieve Complete or Major Molecular Response at 12 months.

End point type	Secondary

End point timeframe:

12 months post-randomisation

End point values	Imatinib alone	Imatinib plus Hydroxychloroquine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percent				
Complete Molecular Response	0	0		
Major Molecular Response	20	23		
No Molecular Response	5	2		
Missing	5	7		

Statistical analyses

Statistical analysis title	12 month molecular response rates

Statistical analysis description:

The comparisons between the study arms of 12 month molecular response rates will use a Mann-Whitney test. A 95% confidence interval for the difference in proportion will be calculated using method 10 in RG Newcombe.

Comparison groups	Imatinib alone v Imatinib plus Hydroxychloroquine
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.43 [6]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Difference in response proportions (%)
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	27.1

Notes:

[5] - 1-sided hypothesis test, set-up to show 12 month molecular response rate is greater in the IM+HCQ arm than the IM alone arm.
[6] - 1-sided

Secondary: 24 month molecular response

End point title	24 month molecular response

End point description:

The proportion of patients who achieve Complete or Major Molecular Response at 12 months.

End point type	Secondary

End point timeframe:

24 months post-randomisation

End point values	Imatinib alone	Imatinib plus Hydroxychloroquine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percent				
Complete Molecular Response	1	2		
Major Molecular Response	19	22		
No Molecular Response	4	1		
Missing	6	7		

Statistical analyses

Statistical analysis title	24 month molecular response rates

Statistical analysis description:

The comparisons between the study arms of 24 month molecular response rates will use a Mann-Whitney test. A 95% confidence interval for the difference in proportion will be calculated using method 10 in RG Newcombe.

Comparison groups	Imatinib alone v Imatinib plus Hydroxychloroquine
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.33 [8]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Difference in response proportions (%)
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	29.7

Notes:

[7] - 1-sided hypothesis test, set-up to show 24 month molecular response rate is greater in the IM+HCQ arm than the IM alone arm.
[8] - 1-sided

Secondary: 12 month progression rates

End point title	12 month progression rates

End point description:

12 month disease progression proportion.

Note that disease progression (suspected or confirmed) was not recorded for any patient, therefore no analyses were performed.

End point type	Secondary

End point timeframe:

12 months post-randomisation

End point values	Imatinib alone	Imatinib plus Hydroxychloroquine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percent				
No evidence of progression	29	30		
Progression suspected	0	0		
Confirmed progression	0	0		

Missing	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: 24 month progression rates

End point title	24 month progression rates

End point description:

24 month disease progression proportion.

Note that disease progression (suspected or confirmed) was not recorded for any patient, therefore no analyses were performed.

End point type	Secondary

End point timeframe:

24 months post-randomisation

End point values	Imatinib alone	Imatinib plus Hydroxychloroquine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percent				
No evidence of progression	29	30		
Progression suspected	0	0		
Confirmed progression	0	0		
Missing	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Imatinib plasma levels (C2D15)

End point title	Imatinib plasma levels (C2D15)

End point description:

Change from baseline in Imatinib plasma levels.

End point type	Secondary

End point timeframe:

Cycle 2, Day 15

End point values	Imatinib plasma population (IM only)	Imatinib plasma population (IM+HCQ)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	20		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	-14 (-119 to 131)	-36 (-283 to 329)		

Statistical analyses

Statistical analysis title	Imatinib plasma levels

Statistical analysis description:

Comparison of change from baseline to cycle 2 day 15 in Imatinib plasma levels between the study arms. The difference between the arms is tested using a Mann-Whitney test. An adjustment for multiple comparisons (timepoints) has been made using the false discovery rate (FDR) approach.

Note - patients who have not consented to blood sampling or have withdrawn consent have also been excluded. Blood samples were not taken for the 12 patients (6 IM alone, 6 IM + HCQ) in the safety run-in period.

Comparison groups	Imatinib plasma population (IM only) v Imatinib plasma population (IM+HCQ)
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 [9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - This is the unadjusted 2-sided p-value. The FDR adjusted 2-sided p-value is 0.93.

Secondary: Imatinib plasma levels (C4D1)

End point title	Imatinib plasma levels (C4D1)

End point description:

Change from baseline in Imatinib plasma levels.

End point type	Secondary

End point timeframe:

Cycle 4, Day 1

End point values	Imatinib plasma population (IM only)	Imatinib plasma population (IM+HCQ)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	17		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	118 (-3 to 368)	69 (-139 to 150)		

Statistical analyses

Statistical analysis title	Imatinib plasma levels

Statistical analysis description:

Comparison of change from baseline to cycle 4 day 1 in Imatinib plasma levels between the study arms. The difference between the arms is tested using a Mann-Whitney test. An adjustment for multiple comparisons (timepoints) has been made using the false discovery rate (FDR) approach.

Note - patients who have not consented to blood sampling or have withdrawn consent have also been excluded. Blood samples were not taken for the 12 patients (6 IM alone, 6 IM + HCQ) in the safety run-in period.

Comparison groups	Imatinib plasma population (IM only) v Imatinib plasma population (IM+HCQ)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - This is the unadjusted 2-sided p-value. The FDR adjusted 2-sided p-value is 0.93.

Secondary: Imatinib plasma levels (C7D1)

End point title	Imatinib plasma levels (C7D1)

End point description:

End point type	Secondary

End point timeframe:

Cycle 7, Day 1

End point values	Imatinib plasma population (IM only)	Imatinib plasma population (IM+HCQ)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	17		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	-41 (-186 to 185)	29 (-289 to 407)		

Statistical analyses

Statistical analysis title	Imatinib plasma levels

Statistical analysis description:

Comparison of change from baseline to cycle 7 day 1 in Imatinib plasma levels between the study arms. The difference between the arms is tested using a Mann-Whitney test. An adjustment for multiple comparisons (timepoints) has been made using the false discovery rate (FDR) approach.

Note - patients who have not consented to blood sampling or have withdrawn consent have also been excluded. Blood samples were not taken for the 12 patients (6 IM alone, 6 IM + HCQ) in the safety run-in period.

Comparison groups	Imatinib plasma population (IM only) v Imatinib plasma population (IM+HCQ)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93 [11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - This is the unadjusted 2-sided p-value. The FDR adjusted 2-sided p-value is 0.93.

Secondary: Imatinib plasma levels (C10D1)

End point title	Imatinib plasma levels (C10D1)

End point description:

Change from baseline in Imatinib plasma levels.

End point type	Secondary

End point timeframe:

Cycle 10, Day 1

End point values	Imatinib plasma population (IM only)	Imatinib plasma population (IM+HCQ)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	16		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	153 (-123 to 330)	165 (-43 to 392)		

Statistical analyses

Statistical analysis title	Imatinib plasma levels

Statistical analysis description:

Comparison of change from baseline to cycle 10 day 1 in Imatinib plasma levels between the study arms. The difference between the arms is tested using a Mann-Whitney test. An adjustment for multiple comparisons (timepoints) has been made using the false discovery rate (FDR) approach.

Note - patients who have not consented to blood sampling or have withdrawn consent have also been excluded. Blood samples were not taken for the 12 patients (6 IM alone, 6 IM + HCQ) in the safety run-in period.

Comparison groups	Imatinib plasma population (IM only) v Imatinib plasma population (IM+HCQ)

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - This is the unadjusted 2-sided p-value. The FDR adjusted 2-sided p-value is 0.93.

Secondary: Imatinib plasma levels (C13D1)

End point title	Imatinib plasma levels (C13D1)

End point description:

Change from baseline in Imatinib plasma levels.

End point type	Secondary

End point timeframe:

Cycle 13, Day 1

End point values	Imatinib plasma population (IM only)	Imatinib plasma population (IM+HCQ)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	15		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	163 (-109 to 659)	268 (-102 to 668)		

Statistical analyses

Statistical analysis title	Imatinib plasma levels

Statistical analysis description:

Comparison of change from baseline to cycle 13 day 1 in Imatinib plasma levels between the study arms. The difference between the arms is tested using a Mann-Whitney test. An adjustment for multiple comparisons (timepoints) has been made using the false discovery rate (FDR) approach.

Note - patients who have not consented to blood sampling or have withdrawn consent have also been excluded. Blood samples were not taken for the 12 patients (6 IM alone, 6 IM + HCQ) in the safety run-in period.

Comparison groups	Imatinib plasma population (IM only) v Imatinib plasma population (IM+HCQ)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - This is the unadjusted 2-sided p-value. The FDR adjusted 2-sided p-value is 0.93.

Secondary: Whole blood HCQ levels

End point title	Whole blood HCQ levels

End point description:

Proportion of IM+HCQ patients achieving HCQ concentrations of >2000ng/ml at any point up to 12 months post-randomisation.

Excludes the 6 IM + HCQ patients in the safety run-in period where blood samples were not taken. Patients who have not consented to blood sampling or have withdrawn consent have also been excluded.

End point type	Secondary

End point timeframe:

Up to 12 months post-randomisation.

End point values	Whole blood HCQ population			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Percent				
Achieved HCQ conc >2000ng/ml	8			
Did not achieve HCQ conc >2000ng/ml	9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded from the date of randomisation and throughout the study period (24 months post-randomisation) and for at least 30 days after discontinuation of protocol specific medication. All AEs were followed until resolution.

Adverse event reporting additional description:

Note - it is not possible to determine the number of occurrences of non-serious AEs from our database. Therefore the number of occurrences of non-serious AEs is assumed to be one per patient.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	IM only safety population
Reporting group description: -	
Reporting group title	IM+HCQ safety population

Reporting group description: -

Serious adverse events	IM only safety population	IM+HCQ safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	5 / 32 (15.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify			
subjects affected / exposed	1 / 29 (3.45%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Intraoperative endocrine injury			
subjects affected / exposed	0 / 29 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heart failure			

subjects affected / exposed	0 / 29 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures - Other, specify			
subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders - Other, specify			

subjects affected / exposed	0 / 29 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal calculi			
subjects affected / exposed	0 / 29 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	IM only safety population	IM+HCQ safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 29 (58.62%)	25 / 32 (78.13%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Vascular disorders - Other, specify			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Oedema face			
subjects affected / exposed	3 / 29 (10.34%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	2 / 29 (6.90%)	6 / 32 (18.75%)	
occurrences (all)	2	6	
Flu like symptoms			
subjects affected / exposed	3 / 29 (10.34%)	3 / 32 (9.38%)	
occurrences (all)	3	3	
General disorders and administration site conditions - Other, specify			
subjects affected / exposed	4 / 29 (13.79%)	5 / 32 (15.63%)	
occurrences (all)	4	5	
Localized oedema			
subjects affected / exposed	9 / 29 (31.03%)	8 / 32 (25.00%)	
occurrences (all)	9	8	
Pain			
subjects affected / exposed	7 / 29 (24.14%)	7 / 32 (21.88%)	
occurrences (all)	7	7	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	4 / 29 (13.79%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 29 (10.34%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Cardiac disorders			
Cardiac disorders - Other, specify			
subjects affected / exposed	2 / 29 (6.90%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 29 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	3 / 29 (10.34%)	4 / 32 (12.50%)	
occurrences (all)	3	4	
Lethargy			
subjects affected / exposed	2 / 29 (6.90%)	5 / 32 (15.63%)	
occurrences (all)	2	5	
Nervous system disorders - Other, specify			
subjects affected / exposed	2 / 29 (6.90%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Paresthesia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Eye disorders			
Blurred vision			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Conjunctivitis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Eye disorders - Other, specify			
subjects affected / exposed	3 / 29 (10.34%)	6 / 32 (18.75%)	
occurrences (all)	3	6	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	4 / 29 (13.79%)	9 / 32 (28.13%)	
occurrences (all)	4	9	
Diarrhoea			
subjects affected / exposed	13 / 29 (44.83%)	22 / 32 (68.75%)	
occurrences (all)	13	22	
Dyspepsia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders - Other, specify			
subjects affected / exposed	4 / 29 (13.79%)	2 / 32 (6.25%)	
occurrences (all)	4	2	
Nausea			
subjects affected / exposed	7 / 29 (24.14%)	15 / 32 (46.88%)	
occurrences (all)	7	15	
Vomiting			
subjects affected / exposed	5 / 29 (17.24%)	7 / 32 (21.88%)	
occurrences (all)	5	7	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	4 / 29 (13.79%)	4 / 32 (12.50%)	
occurrences (all)	4	4	
Pruritus			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	6 / 29 (20.69%)	3 / 32 (9.38%)	
occurrences (all)	6	3	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	4 / 29 (13.79%)	3 / 32 (9.38%)	
occurrences (all)	4	3	
Renal and urinary disorders			
Renal and urinary disorders - Other, specify			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	3 / 29 (10.34%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorder - Other, specify			
subjects affected / exposed	11 / 29 (37.93%)	10 / 32 (31.25%)	
occurrences (all)	11	10	
Musculoskeletal deformity			
subjects affected / exposed	2 / 29 (6.90%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	6 / 29 (20.69%)	10 / 32 (31.25%)	
occurrences (all)	6	10	
Otitis externa			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Rhinitis infective			
subjects affected / exposed	3 / 29 (10.34%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Skin infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Upper respiratory infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2010	Amendment Number 1: Amendment to patient information sheet and protocol. Update to the visit schedule for patients on the Imatinib arm of the trial - these patients were not required to come for weekly visits as they had been on a stable dose of Imatinib for >6 months therefore the protocol and patient information sheet were changed to this effect. Change to the timeline of supportive care for patients with grade 3 nausea, vomiting or diarrhoea from 24 hours to 72 hours made to protocol.
20 October 2010	Amendment Number 2: For information only, change in the product license number of the IMP (Hydroxychloroquine) and clarification provided regarding the repackaging, labelling and distribution of the IMP.
14 March 2011	Amendment Number 5: Changes to protocol to incorporate - change of eligibility criteria to include patients that have been on Imatinib treatment for more than 3 years, increase the number of recruiting sites (addition of 2 new sites), reduction in the number of eye exams based on review of the eye toxicity data, and other minor administrative changes to the protocol.
20 September 2011	Amendment Number 6: Protocol amendment to remove a number of the screening tests which were considered unnecessary and hindering recruitment to the trial and other minor administrative changes.
08 December 2011	Amendment Number 7: Changes to protocol and provision of further patient information documentation around the visual acuity tests included within the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported