Clinical trial results:
WT1 Immunity via DNA fusion Gene Vaccination in Haematological Malignancies by intramuscular injection followed by intramuscular electroporation.

Summary

EudraCT number	2009-017340-14
Trial protocol	GB
Global end of trial date	04 June 2014

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	RHMCAN0700

Additional study identifiers

ISRCTN number	ISRCTN62678383
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ISRCTN reference number : ISRCTN62678383, Gene Therapy Advisory Committee reference number: 173

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation Trust
Sponsor organisation address	Southampton General Hospital, Level E, Laboratory & Pathology Block, SCBR, MP 138, Southampton, United Kingdom, SO16 6YD
Public contact	University of Southampton Clinical Trials Unit, University of Southampton Clinical Trials Unit, 0044 2381205154, ctu@soton.ac.uk
Scientific contact	University of Southampton Clinical Trials Unit, University of Southampton Clinical Trials Unit, 0044 2381205154, ctu@soton.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	21 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The principal research questions are:

a) In patients with chronic myeloid leukemia (CML) whether WT1 DNA vaccination can reduce the measurable amount of the leukaemia-derived marker (BCR-ABL and WT-1transcripts), of which BCR-ABL is already used for clinical monitoring of disease response and decision making.

b) In patients with acute myeloid leukemia (AML) to examine the effect of WT1 DNA vaccination on time to disease progression in a patient group that has a 70% risk of disease recurrence in 2 years.

Protection of trial subjects:

Painkillers (eg. paracetamol) were provided if needed. Of note, this was not necessary for any patient in the study GTAC 089.

At all visits the physical examination included a careful examination of the injection site including measurements of the circumference of the extremity where appropriate if there was clinical evidence of a local reaction. Patients were monitored throughout the study period for anti-DNA antibodies, rheumatoid factors and evidence of muscle destruction. Levels of anti-DNA antibodies and rheumatoid factors were measured according to standard local ranges. If these tests became significantly positive, after previously being absent or normal or other clinically significant signs of autoimmunity appear, vaccination would have been terminated and rheumatology consultation sought.

For all patients pain or discomfort and level of distress was assessed 1 hr after injection (or after recovery from sedation) and at 48 hrs. The information was collected using questionnaires.

Vital signs were monitored closely after administration of the DNA. If anaphylaxis occurs, the patient were treated immediately, initially with adrenaline, hydrocortisone and chlorpheniramine.

If CTC toxicity grade>2 occurs in a particular patient, vaccination were to be paused. Further vaccination may have been offered after normalization if appropriate in the opinion of the treating clinician and only after documented discussion with the UoSCTU and lead investigators.

Background therapy:

Steroids or other drugs with a likely effect on immune competence are not permitted during the course of the trial. Concomitant medication may be given as medically indicated. Patients with CML-CP will continue on tyrosine kinase inhibitor therapy.

Evidence for comparator:

Patients with HLA A2-ve genotype were not vaccinated and formed the control group.

Actual start date of recruitment	01 February 2011
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	18
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 1st February 2011 and 26th February 2013, 23 CML patients were registered from three UK hospitals (Southampton General Hospital, Hammersmith Hospital and Royal Devon and Exeter Hospital). The CML arm of the trial was terminated early by the funders due to poor recruitment and therefore the AML arm were not opened to recruitment.

Pre-assignment

Screening details:

Screening details given in the pre-assignment period

Pre-assignment period milestones

Number of subjects started	91[1]
Number of subjects completed	22

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not eligible: 47
Reason: Number of subjects	Patient choice: 7
Reason: Number of subjects	Other: 2
Reason: Number of subjects	Unknown: 12
Reason: Number of subjects	Physician decision: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Pre-assignment period includes all patients assessed for eligibility and is therefore greater than the number actually enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	HLA A2 positive

Arm description:

Intervention group: all eligible, consenting CML patients who were HLA A2 positive

Arm type	Experimental
Investigational medicinal product name	p.DOM-WT1-37
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

p.DOM-WT1-37: 1mg/dose/vaccine
The DNA vaccine was administered 6 times every 4 weeks followed by a further 6 vaccinations every 3 months to maximum of 24 months.

Investigational medicinal product name	p.DOM-WT1-126
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

p.DOM-WT1-126: 1mg/dose/vaccine
The DNA vaccine will be administered 6 times every 4 weeks followed by a further 6 vaccinations every 3 months to maximum of 24 months.

Arm title	HLA A2 Negative

Arm description:

Control group: all eligible and consenting patients who were HLA A2 negative

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[2]	HLA A2 positive	HLA A2 Negative
Started	13	9
Completed	4	2
Not completed	9	7
Physician decision	1	-
Consent withdrawn by subject	6	5
Imatinib dose decreased	2	-
Changed to dasatinib	-	1
Other medical urgent issues	-	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient was enrolled but excluded before baseline period and HLA A2 status obtained due to achieving CMR

Baseline characteristics

Reporting groups	
Reporting group title	HLA A2 positive
Reporting group description:	
Intervention group: all eligible, consenting CML patients who were HLA A2 positive	
Reporting group title	HLA A2 Negative
Reporting group description:	
Control group: all eligible and consenting patients who were HLA A2 negative	

Reporting group values	HLA A2 positive	HLA A2 Negative	Total
Number of subjects	13	9	22
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 Units: years			
median	52	56	
full range (min-max)	23 to 66	42 to 73	-
Gender categorical Units: Subjects			
Female	7	4	11
Male	6	4	10
Not recorded	0	1	1
BCR-ABL Transcript type Units: Subjects			
e13/e14a2	0	1	1
e13a2	2	3	5
e13a2/e14a2	0	1	1
e14a2	7	2	9
unknown	3	1	4
Not analysed	1	1	2
BCR_ABL Result Units: Subjects			
Positive	12	8	20
Undetectable	0	0	0
Failed	0	0	0
Not analysed	1	1	2
WT1 result			

Units: Subjects			
Positive	12	7	19
Undetectable	0	1	1
Failed	0	0	0
Not analysed	1	1	2

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All registered patients who obtained an HLA A2 status following the intention-to-treat principle.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

For safety analyses, all patients with positive HLA A2 status who received at least one trial drug administration were evaluable for toxicity. All controls (HLA A2 negative) were included in the safety analyses, where relevant.

Subject analysis set title	Molecular analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The analyses on molecular response were performed on all patients with molecular data at a minimum of 2 post-baseline time points (HLA A2 positive patients must also have received at least 1 dose of the vaccine).

Reporting group values	ITT population	Safety analysis set	Molecular analysis set
Number of subjects	22	21	20
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 Units: years			
median	53	52	53
full range (min-max)	23 to 73	23 to 73	23 to 73
Gender categorical Units: Subjects			
Female	11	10	10
Male	10	10	10
Not recorded	1	1	0
BCR-ABL Transcript type Units: Subjects			
e13/e14a2	1	1	1
e13a2	5	5	5

e13a2/e14a2	1	1	1
e14a2	9	9	9
unknown	4	5	4
Not analysed	2	1	0
BCR_ABL Result Units: Subjects			
Positive	20	20	20
Undetectable	0	0	0
Failed	0	0	0
Not analysed	2	1	0
WT1 result Units: Subjects			
Positive	19	19	19
Undetectable	1	1	1
Failed	0	0	0
Not analysed	2	1	0

End points

End points reporting groups

Reporting group title	HLA A2 positive
Reporting group description:	
Intervention group: all eligible, consenting CML patients who were HLA A2 positive	
Reporting group title	HLA A2 Negative
Reporting group description:	
Control group: all eligible and consenting patients who were HLA A2 negative	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All registered patients who obtained an HLA A2 status following the intention-to-treat principle.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
For safety analyses, all patients with positive HLA A2 status who received at least one trial drug administration were evaluable for toxicity. All controls (HLA A2 negative) were included in the safety analyses, where relevant.	
Subject analysis set title	Molecular analysis set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The analyses on molecular response were performed on all patients with molecular data at a minimum of 2 post-baseline time points (HLA A2 positive patients must also have received at least 1 dose of the vaccine).	

Primary: Molecular response of BCR-ABL (major or minor response or CMR)

End point title	Molecular response of BCR-ABL (major or minor response or CMR)
End point description:	
1) For patients with a baseline BCR-ABL transcript level less than 11: CMR: 0 BCR-ABL transcript level with ABL control copy greater than or equal to 32,000; in TWO CONSECUTIVE tests. These patients cannot be assessed for a major or minor response as defined below. 2) For patients with a baseline BCR-ABL transcript level greater than or equal to 11: a. CMR: 0 BCR-ABL transcript level with ABL control copy greater than or equal to 32,000; in TWO CONSECUTIVE tests. b. Major response: a fall greater than 1 log in the BCR-ABL transcript level ratio.* c. Minor response: a fall greater than 0.5 log in the BCR-ABL transcript level ratio.* *Confirmed in an ABL control copy greater than or equal to 32,000 in two consecutive samples at any time during follow up.	
End point type	Primary
End point timeframe:	
Molecular samples collected during various follow up visits and compared to the baseline sample. Only responses measured at weeks 4, 8, 12, 16, 20, 32 and 11, 17 and 23 months were considered in the analysis as pre-defined in the protocol.	

End point values	HLA A2 positive	HLA A2 Negative	Molecular analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12[1]	8[2]	20	
Units: Number				
BCR-ABL response (CMR or minor or major)	1	1	2	
BCR-ABL no response (CMR or minor or major)	11	7	18	

Notes:

[1] - Number in molecular analysis population

[2] - Number in molecular analysis population

Statistical analyses

Statistical analysis title	Fisher's exact test

Statistical analysis description:

Fisher’s exact test was used to compare differences in proportions of molecular response in CML patients versus controls.

Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	Fisher exact

Secondary: Molecular response of BCR-ABL response (major or CMR)

End point title	Molecular response of BCR-ABL response (major or CMR)

End point description:

1) For patients with a baseline BCR-ABL transcript level less than 11:
CMR: 0 BCR-ABL transcript level with ABL control copy greater than or equal to 32,000; in TWO CONSECUTIVE tests.
These patients cannot be assessed for a major or minor response as defined below.

2) For patients with a baseline BCR-ABL transcript level greater than or equal to 11:
a. CMR: 0 BCR-ABL transcript level with ABL control copy greater than or equal to 32,000; in TWO CONSECUTIVE tests.
b. Major response: a fall greater than 1 log in the BCR-ABL transcript level ratio.*

*Confirmed in an ABL control copy greater than or equal to 32,000 in two consecutive samples at any time during follow up.

End point type	Secondary

End point timeframe:

Molecular samples collected during various follow up visits and compared to the baseline sample.

Only responses measured at weeks 4, 8, 12, 16, 20, 32 and 11, 17 and 23 months were considered in the analysis as pre-defined in the protocol.

End point values	HLA A2 positive	HLA A2 Negative	Molecular analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12[3]	8[4]	20	
Units: Number				
BCR-ABL response (CMR or major)	1	1	2	
BCR-ABL no response (CMR or major)	11	7	18	

Notes:

[3] - Number in molecular analysis population

[4] - Number in molecular analysis population

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	> 0.999
Method	Fisher exact

Notes:

[5] - Fisher’s exact test was used to compare differences in proportions of molecular response in CML patients versus controls.

Secondary: Molecular response of WT1 (CMR or minor or major)

End point title	Molecular response of WT1 (CMR or minor or major)

End point description:

1) For patients with a baseline WT1/GUS ratio less than 0.1%:
a) CMR: 0% WT1/GUS ratio with GUS control copy greater than or equal to 32,000; in TWO CONSECUTIVE tests.
b) These patients cannot be assessed for a major or minor response as defined below.

2) For patients with a baseline WT1/GUS ratio greater than or equal to 0.1%:
a) CMR: 0% WT1/GUS ratio with GUS control copy greater than or equal to 32,000; in TWO CONSECUTIVE tests.
b) Major response: a fall greater than 1 log in the WT1/GUS ratio.*
c) Minor response: a fall greater than 0.5 log in the WT1/GUS ratio.*

*Confirmed in a GUS control copy greater than or equal to 32,000 in two consecutive samples at any time during follow up.

End point type	Secondary

End point timeframe:

Molecular samples collected during various follow up visits and compared to the baseline sample.

Only responses measured at weeks 4, 8, 12, 16, 20, 32 and 11, 17 and 23 months were considered in the analysis as pre-defined in the protocol.

End point values	HLA A2 positive	HLA A2 Negative	Molecular analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12[6]	8[7]	20	
Units: Number				
WT1 response (CMR or minor or major)	2	1	3	

WT1 no response (CMR or minor or major)	10	7	17	

Notes:

[6] - Number in molecular analysis set

[7] - Number in molecular analysis population

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	HLA A2 Negative v HLA A2 positive v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	> 0.999
Method	Fisher exact

Notes:

[8] - Fisher’s exact test was used to compare differences in proportions of molecular response in CML patients versus controls.

Secondary: Time to disease progression

End point title	Time to disease progression

End point description:

Disease progression for CML patients is defined as a loss in complete haematological response, where at least one factor falls out of the following ranges 56:

- o WBC < 10 x 109/L
- o Basophils < 5%
- o No myelocytes, promyelocytes, myeloblasts in the differential
- o Platelet count < 450 x 109/L
- o Spleen nonpalpable

End point type	Secondary

End point timeframe:

Time to disease progression was defined as time from date of consent to date of progression, last follow up or death (whichever occurs first). Patients who die and do not progress are censored at the date of death/last follow up.

End point values	HLA A2 positive	HLA A2 Negative	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13[9]	9[10]	22[11]	
Units: Months				
median (confidence interval 90%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Notes:

[9] - No events observed therefore median and CI not reached

[10] - No events observed therefore median and CI not reached

[11] - No events observed therefore median and CI not reached

Attachments (see zip file)	Kaplan-Meier for time to progression or death /WIN PFS KM

Statistical analyses

Statistical analysis title	Cox proportional hazards regression

Statistical analysis description:

No events observed so therefore no results were computed.

Comparison groups	HLA A2 positive v HLA A2 Negative v ITT population
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1

Notes:

[12] - No events observed so therefore no results were computed. Dummy values entered to satisfy upload

Secondary: Time to next treatment

End point title	Time to next treatment

End point description:

A next treatment is defined as the first drug taken during the course of the study with an indication to treat CML.

End point type	Secondary

End point timeframe:

Time to next treatment defined as time from date of consent to date of last follow up or next CML treatment (whichever occurs first). Patients who die or do not have a next treatment are censored at the date of death/last follow up.

End point values	HLA A2 positive	HLA A2 Negative	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13[13]	9[14]	22[15]	
Units: Months				
median (confidence interval 90%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Notes:

[13] - No events observed therefore median and CI not reached

[14] - No events observed therefore median and CI not reached

[15] - No events observed therefore median and CI not reached

Attachments (see zip file)	Kaplan-Meier for time to next treatment /WIN Time to next

Statistical analyses

Statistical analysis title	Cox proportional hazard regression

Statistical analysis description:

The reference category for the Hazard Ratio is HLA A2 - patients i.e. a hazard ratio greater than 1 represents a favourable outcome for HLA A2 - patients; a hazard ratio below 1 represents a favourable outcome for HLA A2 + patients

No results were computed as no events were observed.

Comparison groups	HLA A2 positive v HLA A2 Negative v ITT population
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [16]
Method	Not done
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1

Notes:

[16] - No results were computed as no events were observed. dummy value entered to satisfy upload

Secondary: Time to BCR-ABL response (major or minor or CMR) from the beginning of tyrosine kinase inhibitor treatment

End point title	Time to BCR-ABL response (major or minor or CMR) from the beginning of tyrosine kinase inhibitor treatment

End point description:

Patients who did not respond were censored at the date of last BCR-ABL response.

End point type	Secondary

End point timeframe:

Time to BCR-ABL response in years is defined as time from date of beginning tyrosine kinase inhibitor treatment to date of last BCR-ABL sample or the first date of BCR-ABL response (whichever occurs first).

End point values	HLA A2 positive	HLA A2 Negative	Molecular analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12[17]	8[18]	20[19]	
Units: Years				
median (confidence interval 90%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Notes:

[17] - The number in the molecular analysis population

[18] - The number in the molecular analysis population

[19] - Median and CI were not reached due to small number of events

Attachments (see zip file)	Kaplan-Meier plot/WIN Time to BCR-ABL response from

Statistical analyses

Statistical analysis title	Cox proportional hazards model

Statistical analysis description:

The reference category for the Hazard Ratio is HLA A2 - patients i.e. a hazard ratio greater than 1 represents a favourable outcome for HLA A2 - patients; a hazard ratio below 1 represents a favourable outcome for HLA A2 + patients

Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.77
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.661
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.064
upper limit	6.782

Notes:

[20] - Median time and its 90% confidence interval were not reached because a small number of events were observed.

Statistical analysis title	Logrank test
Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768
Method	Logrank

Secondary: Time to BCR-ABL response (major or minor or CMR) from date of informed consent

End point title	Time to BCR-ABL response (major or minor or CMR) from date of informed consent

End point description:

End point type	Secondary

End point timeframe:

Time to BCR-ABL response in months is defined as time from date of consent to date of last BCR-ABL sample or the first date of BCR-ABL response (whichever occurs first). Patients who did not respond were censored at the date of last BCR-ABL response.

End point values	HLA A2 positive	HLA A2 Negative	Molecular analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12[21]	8[22]	20[23]	
Units: Months				
median (confidence interval 90%)	0 (0 to 0)	22.8 (22.8 to 100)	22.8 (22.8 to 100)	

Notes:

[21] - Number in molecular analysis population
Median & CI not reached

[22] - Number in molecular analysis population
Median & CI not reached

[23] - Median and upper CI not reached due to small number of events.

Attachments (see zip file)	Kaplan-Meier plot/WIN Time to BCR-ABL response from date of

Statistical analyses

Statistical analysis title	Cox proportional hazard regression
Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.699
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.577
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.056
upper limit	5.947

Statistical analysis title	Logrank test
Comparison groups	HLA A2 Negative v HLA A2 positive v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.695
Method	Logrank

Secondary: Time to WT1 response (major or minor or CMR) in years is defined as time from date of beginning tyrosine kinase inhibitor treatment

End point title	Time to WT1 response (major or minor or CMR) in years is defined as time from date of beginning tyrosine kinase inhibitor treatment

End point description:

Patients who did not respond were censored at the date of last WT1 response.

End point type	Secondary

End point timeframe:

Time to WT1 response in years is defined as time from date of beginning tyrosine kinase inhibitor treatment to date of last WT1 sample or the first date of WT1 response (whichever occurs first).

End point values	HLA A2 positive	HLA A2 Negative	Molecular analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12[24]	8[25]	20[26]	
Units: Years				
median (confidence interval 90%)	8 (8 to 100)	8.7 (8.7 to 100)	8.7 (8.7 to 100)	

Notes:

[24] - Median and Upper CI not reached. numbers added for compliance. see KM plot

[25] - Median and Upper CI not reached. numbers added for compliance. see KM plot

[26] - Median and upper CI not reached due to small number of events.
Numbers added for compliance

Attachments (see zip file)	Kaplan-Meier plot/WIN Time to WT1 response from beginning

Statistical analyses

Statistical analysis title	Cox proportional hazard regression

Statistical analysis description:

The reference category for the Hazard Ratio is HLA A2 - patients i.e. a hazard ratio greater than 1 represents a favourable outcome for HLA A2 - patients; a hazard ratio below 1 represents a favourable outcome for HLA A2 + patients

Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.765
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.688
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.088
upper limit	5.397

Statistical analysis title	Logrank test
Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.764
Method	Logrank

Secondary: Time to WT1 response (major or minor or CMR) from date of informed consent

End point title	Time to WT1 response (major or minor or CMR) from date of informed consent

End point description:

Patients who did not respond were censored at the date of last WT1 response.

End point type	Secondary

End point timeframe:

Time to WT1 response in months is defined as time from date of consent to date of last WT1 sample or the first date of WT1 response (whichever occurs first).

End point values	HLA A2 positive	HLA A2 Negative	Molecular analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12[27]	8[28]	20[29]	
Units: Months				
median (confidence interval 90%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Notes:

[27] - Number in the molecular analysis population

[28] - Number in the molecular analysis population

[29] - Median and CI not reached due to small number of events.

Attachments (see zip file)	Kaplan-Meier plot/WIN Time to WT1 response from date of

Statistical analyses

Statistical analysis title	Cox proportional hazards regression
Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.879
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.205
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.161
upper limit	9.05

Statistical analysis title	Logrank test
Comparison groups	HLA A2 positive v HLA A2 Negative v Molecular analysis set

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.879
Method	Logrank

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

OS defined as time from date of consent to date of last follow up or death (whichever occurs first). Patients who do not die are censored at the date of last follow up.

End point values	HLA A2 positive	HLA A2 Negative	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	9	22[30]	
Units: Months				
median (confidence interval 90%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Notes:

[30] - Median and CI not reached due to no events observed.

Attachments (see zip file)	Kaplan-Meier plot/WIN OS KM plot.png

Statistical analyses

Statistical analysis title	Cox proportional hazard regression

Statistical analysis description:

No events observed so therefore no results were computed.

Comparison groups	HLA A2 positive v HLA A2 Negative v ITT population
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [31]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1

Notes:

[31] - No events observed so therefore no results were computed.

Secondary: Pain assessment immediately after vaccination (How severe is your pain or discomfort now?)

End point title	Pain assessment immediately after vaccination (How severe is your pain or discomfort now?)[32]

End point description:

Pain and discomfort data were collected on a visual analogue scale ranging from 0 (no pain/discomfort) to 10 (worst ever pain/discomfort).
Median score for each pain assessment question obtained by calculating the summary statistics using the median score for the corresponding pain assessment question recorded for each patient across all vaccination visits .

End point type	Secondary

End point timeframe:

Recorded immediately after vaccination

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain assessment information recorded immediately after vaccination and recorded 48 hours post
vaccination were summarised in terms of the median pain score recorded and the worst pain score recorded for HLA A2+ patients in the ITT population only.

End point values	HLA A2 positive			
Subject group type	Reporting group			
Number of subjects analysed	12[33]			
Units: Score from 0 (none) to 10 (worst)				
median (inter-quartile range (Q1-Q3))	1 (1 to 2.3)			

Notes:

[33] - One patient did not receive any treatment and therefore was not included in summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment immediately after vaccination (How severe was your pain or discomfort during and immediately after the injection?)

End point title	Pain assessment immediately after vaccination (How severe was your pain or discomfort during and immediately after the injection?)[34]

End point description:

Pain and discomfort data were collected on a visual analogue scale ranging from 0 (no pain/discomfort) to 10 (worst ever pain/discomfort).
Median score for each pain assessment question obtained by calculating the summary statistics using the median score for the corresponding pain assessment question recorded for each patient across all vaccination visits .

End point type	Secondary

End point timeframe:

Assessment completed immediately post-vaccination

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain assessment information recorded immediately after vaccination and recorded 48 hours post
vaccination were summarised in terms of the median pain score recorded and the worst pain score recorded for HLA A2+ patients in the ITT population only.

End point values	HLA A2 positive			
Subject group type	Reporting group			
Number of subjects analysed	12[35]			
Units: Score from 0 (none) to 10 (worst)				
median (inter-quartile range (Q1-Q3))	3 (2 to 5)			

Notes:

[35] - One patient did not receive any treatment and therefore was not included in summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment immediately after vaccination (How distressing is your pain or discomfort now?)

End point title	Pain assessment immediately after vaccination (How distressing is your pain or discomfort now?)[36]

End point description:

Pain and discomfort data were collected on a visual analogue scale ranging from 0 (no pain/discomfort) to 10 (worst ever pain/discomfort).
Median score for each pain assessment question obtained by calculating the summary statistics using the median score for the corresponding pain assessment question recorded for each patient across all vaccination visits .

End point type	Secondary

End point timeframe:

Assessment completed immediately post-vaccination

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain assessment information recorded immediately after vaccination and recorded 48 hours post
vaccination were summarised in terms of the median pain score recorded and the worst pain score recorded for HLA A2+ patients in the ITT population only.

End point values	HLA A2 positive			
Subject group type	Reporting group			
Number of subjects analysed	12[37]			
Units: Score from 0 (none) to 10 (worst)				
median (inter-quartile range (Q1-Q3))	1 (0.3 to 1)			

Notes:

[37] - One patient did not receive treatment and therefore was excluded from summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment immediately after vaccination (How distressing was your pain or discomfort during and immediately after the injection?)

End point title	Pain assessment immediately after vaccination (How distressing was your pain or discomfort during and immediately after the injection?)[38]

End point description:

Pain and discomfort data were collected on a visual analogue scale ranging from 0 (no pain/discomfort) to 10 (worst ever pain/discomfort).
Median score for each pain assessment question obtained by calculating the summary statistics using the median score for the corresponding pain assessment question recorded for each patient across all vaccination visits .

End point type	Secondary

End point timeframe:

Assessment completed immediately post-vaccination

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain assessment information recorded immediately after vaccination and recorded 48 hours post
vaccination were summarised in terms of the median pain score recorded and the worst pain score recorded for HLA A2+ patients in the ITT population only.

End point values	HLA A2 positive			
Subject group type	Reporting group			
Number of subjects analysed	12[39]			
Units: Score from 0 (none) to 10 (worst)				
median (inter-quartile range (Q1-Q3))	2.3 (1 to 4)			

Notes:

[39] - One patient did not receive treatment and therefore was excluded from summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment 48 hours post-vaccination (Pain at its worst in the last 48 hours?)

End point title	Pain assessment 48 hours post-vaccination (Pain at its worst in the last 48 hours?)[40]

End point description:

Pain and discomfort data were collected on a visual analogue scale ranging from 0 (no pain/discomfort) to 10 (worst ever pain/discomfort).
Median score for each pain assessment question obtained by calculating the summary statistics using the median score for the corresponding pain assessment question recorded for each patient across all vaccination visits .

End point type	Secondary

End point timeframe:

Assessment completed 48 hours post-vaccination

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain assessment information recorded immediately after vaccination and recorded 48 hours post
vaccination were summarised in terms of the median pain score recorded and the worst pain score recorded for HLA A2+ patients in the ITT population only.

End point values	HLA A2 positive			
Subject group type	Reporting group			
Number of subjects analysed	12[41]			
Units: Score from 0 (none) to 10 (worst)				
median (inter-quartile range (Q1-Q3))	0.5 (0 to 1)			

Notes:

[41] - One patient did not receive treatment and therefore was excluded from summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment 48 hours post-vaccination (Pain at its least in the last 48 hours?)

End point title	Pain assessment 48 hours post-vaccination (Pain at its least in the last 48 hours?)[42]

End point description:

Pain and discomfort data were collected on a visual analogue scale ranging from 0 (no pain/discomfort) to 10 (worst ever pain/discomfort).
Median score for each pain assessment question obtained by calculating the summary statistics using the median score for the corresponding pain assessment question recorded for each patient across all vaccination visits .

End point type	Secondary

End point timeframe:

Assessment completed 48 hours post-vaccination

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain assessment information recorded immediately after vaccination and recorded 48 hours post
vaccination were summarised in terms of the median pain score recorded and the worst pain score recorded for HLA A2+ patients in the ITT population only.

End point values	HLA A2 positive			
Subject group type	Reporting group			
Number of subjects analysed	12[43]			
Units: Score from 0 (none) to 10 (worst)				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)			

Notes:

[43] - One patient did not receive treatment and therefore was excluded from summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment 48 hours post-vaccination (Pain at its average in the last 48 hours?)

End point title	Pain assessment 48 hours post-vaccination (Pain at its average in the last 48 hours?)[44]

End point description:

Pain and discomfort data were collected on a visual analogue scale ranging from 0 (no pain/discomfort) to 10 (worst ever pain/discomfort).
Median score for each pain assessment question obtained by calculating the summary statistics using the median score for the corresponding pain assessment question recorded for each patient across all vaccination visits .

End point type	Secondary

End point timeframe:

Assessment completed 48 hours post-vaccination

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain assessment information recorded immediately after vaccination and recorded 48 hours post
vaccination were summarised in terms of the median pain score recorded and the worst pain score recorded for HLA A2+ patients in the ITT population only.

End point values	HLA A2 positive			
Subject group type	Reporting group			
Number of subjects analysed	12[45]			
Units: Score from 0 (none) to 10 (worst)				
median (inter-quartile range (Q1-Q3))	0.3 (0 to 1)			

Notes:

[45] - One patient did not receive treatment and therefore was excluded from summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment 48 hours post-vaccination (How much pain you have right now?)

End point title	Pain assessment 48 hours post-vaccination (How much pain you have right now?)[46]

End point description:

Pain and discomfort data were collected on a visual analogue scale ranging from 0 (no pain/discomfort) to 10 (worst ever pain/discomfort).
Median score for each pain assessment question obtained by calculating the summary statistics using the median score for the corresponding pain assessment question recorded for each patient across all vaccination visits .

End point type	Secondary

End point timeframe:

Assessment completed 48 hours post-vaccination

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pain assessment information recorded immediately after vaccination and recorded 48 hours post
vaccination were summarised in terms of the median pain score recorded and the worst pain score recorded for HLA A2+ patients in the ITT population only.

End point values	HLA A2 positive			
Subject group type	Reporting group			
Number of subjects analysed	12[47]			
Units: Score from 0 (none) to 10 (worst)				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)			

Notes:

[47] - One patient did not receive treatment and therefore was excluded from summary.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were reported for the entire trial period. The reporting requirement for SAEs affecting subjects applies for all events which occurred up to 4 weeks after the last administration of study drugs

Adverse event reporting additional description:

Adverse events were assessed during every patient visit.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	HLA A2 positive safety population

Reporting group description:

Intervention group: all eligible, consenting CML patients who were HLA A2 positive and received at least one trial drug administration

Reporting group title	HLA A2 Negative

Reporting group description:

Control group: all eligible and consenting patients who were HLA A2 negative

Serious adverse events	HLA A2 positive safety population	HLA A2 Negative	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	HLA A2 positive safety population	HLA A2 Negative	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	9 / 9 (100.00%)	
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	4 / 12 (33.33%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Epistaxis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders, Other			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Investigations			
CPK increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	2 / 12 (16.67%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications, Other			
subjects affected / exposed	2 / 12 (16.67%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	4	
Nervous system disorders, Other			
subjects affected / exposed	1 / 12 (8.33%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Ear and labyrinth disorders			
Ear and labyrinth disorders, Other			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye disorders, Other			
subjects affected / exposed	2 / 12 (16.67%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Watering eyes			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Bloating			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders, Other			
subjects affected / exposed	2 / 12 (16.67%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Skin ulceration			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal and urinary disorders, Other			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal calculi			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Urinary tract pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders, Other			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	3 / 12 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Eye infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nail infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Upper respiratory infection			
subjects affected / exposed	2 / 12 (16.67%)	5 / 9 (55.56%)	
occurrences (all)	2	6	
Metabolism and nutrition disorders			
Anorexia			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2010	Addition of electrocardiogram at baseline; Logistical changes made for supply and return of IMP; Clarification on monitoring.
01 November 2010	Update in the Investigational Medicinal Product Dossier included in the protocol.
12 August 2011	Clarification of patient pathway throughout the trial from consent; clarification on the schedule of observations and procedure for HLA negative participants; clarification on inclusion criteria for AML patients with regards to WT1 status; clarification determination of bone status for trial inclusion; clarification on resupply of IMP to sites; clarification of local and central laboratory responsibilities and shipment of samples; amendment of pain assessment Case Report Form to remove patient identifiers; addition of DTH (delayed type hypersensitivity) reaction to be carried out wherever feasible.
16 January 2012	Eligibility criteria amended to allow patients with a 6 months history of lymphocyte counts of just below 1 to be included in the trial.
17 May 2012	Stability data for pDOM WT1 DNA vaccines to support the proposed expiry date extension plan at the predetermined 18 month time point.
08 November 2012	Eligibility criteria widened to include all tyrosine kinase inhibitors to increase recruitment; Change in trial design from a two stage design to a single stage design; sample size adjusted to 32 CML patients and 37 AML patients; All HLA A2+ patients to receive all 12 vaccinations instead of only receiving the latter 6 if a response is observed.
07 November 2013	Patients last follow 12 months post final vaccination. ELISPOT removed from endpoint analysis (replaced by tetramer staining). 36 month follow-up visit removed.
03 April 2014	End of Trial Notification

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 April 2013	CML arm of the trial stopped and temporary halt on trial for AML arm.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study did not complete recruitment as per the sample size.

Notes: