Clinical trial results:
Study of apoptosis related changes and endothelial responses of multiple myeloma patients treated with chemotherapy.

Summary

EudraCT number	2012-001813-17
Trial protocol	GB
Global end of trial date	07 November 2017

Results information

Result version number	v1 (current)
This version publication date	11 August 2019
First version publication date	11 August 2019
Summary attachment (see zip file)	Study summary (Apoptosis Study summary.doc) Chemotherapy treatment of multiple myeloma patients increases circulating levels of endothelial micovesicles (Thrombosis Research 2016.pdf)

Trial information

Trial identification

Sponsor protocol code	R1282

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 12/YH/0328

Notes:

Sponsors

Sponsor organisation name	Hull and East Yorkshire Hospitals NHS Trust
Sponsor organisation address	Anlaby Road, Hull, United Kingdom, HU3 2JZ
Public contact	Professor A Maraveyas , Hull and East Yorkshire Hospitals NHS Trust, 044 01482461245, anthony.maraveyas@hey.nhs.uk
Scientific contact	Professor A Maraveyas , Hull and East Yorkshire Hospitals NHS Trust, 044 01482461245, anthony.maraveyas@hey.nhs.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	08 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 November 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To study the disruption of the endothelium, platelets and the clotting cascade caused by the novel chemotherapeutic combinations used for the treatment of multiple myeloma.

Protection of trial subjects:

No risks relating to IMPs as the study was non-interventional and did not influence the treatment or management of the patient. Only risks to subjects were the further blood draws to those that were required under standard of care and confidentiality from data collection. Both of which were managed under the hospitals Standard Operating Procedures and GCP and highlighted in the Ethics submission. No SAEs were experienced due to the blood draws and no issues relating to confidentiality were identified.

Background therapy:

Study was non-interventional (there was no IMP tested either on its own or as a comparator). Study procedures did not influence the treatment or management of the patient. Patients were treated under the standard of care for their disease (myeloma). The standard of care was relevant to the line of treatment that the patient was to receive.

Evidence for comparator:

There was no IMP tested either on its own or as a comparator.

Actual start date of recruitment	11 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	40
From 65 to 84 years	0
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This was a single site study (Castle Hill Hospital - UK) with recruitment commencing from 11/10/2012 to 14/12/2016. Patients were identified in MDT when discussion for their management took place. If a patient was deemed eligible the patient was then approached during their clinical appointment at the Queens Centre for Oncology and Haematology.

Pre-assignment

Screening details:

Patients were approached in clinic following discussion in MDT when need for treatment was determined, whether a initial diagnosis, a relapse of the Myeloma, or if the patient was to be a control. The criteria used to determine each group was detailed in the protocol. No specific pre-assignment period detailed for the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Newly diagnosed MM patients: CTD

Arm description:

Newly diagnosed MM patients treated with Cyclophosphamide Thalidomide & Dexamethasone. Treatment allocation NOT determined by study

Arm type	Standard chemotherapy treatment given
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	PL 00032/0335
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg orally Days 1, 8 and 15

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	EU/1/08/443/001
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Thalidomide 50mg hard capsules orally, initially 100mg daily for 3 weeks, increasing to 200mg daily.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	PL0065/5045R
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg daily orally on Days 1-4 and 12-15

Arm title	Newly diagnosed MM patients: other

Arm description:

Newly Diagnosed MM patients who were to receive treatment other than CTD. Treatment allocation NOT

determined by study

Arm type	Standard chemotherapy treatment given
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	PL 00032/0335
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg orally on Days 1 and 8 of 28 day cycle.

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	EU/1/07/391
Other name	Revlimid
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25mg orally daily on Days 1 - 21

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	PL0065/5045R
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg daily orally on Days 1 - 4 and 12.-15

Arm title	Relapsed MM patients: BTZ+DEX

Arm description:

Relapsed MM Patients to undergo Velcade & Dexamethasone. Treatment allocation NOT determined by study

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Relapsed MM patients: LEN+DEX

Arm description:

Relapsed MM Patients to undergo Lenalidomide & Dexamethasone. Treatment allocation NOT determined by study

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Controls: Myeloproliferative disorders

Arm description:

Patients with myeloproliferative disorders have a known propensity to develop thromboses (non treatment related) and will serve as the positive control group for this study. There are three major categories of myeloproliferative disorders: Chronic myelocytic leukemia, polycythemia rubra vera and myelofibrosis. These patients are followed up in a regular clinic in haematology outpatients. Based on the expected age and gender distribution of the experimental group ten of these control patients will be approached for consent in to the study. The same exclusion criteria (3.1.3) as for the experimental group will be adhered to. Treatment allocation NOT determined by study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Newly diagnosed MM patients: CTD	Newly diagnosed MM patients: other	Relapsed MM patients: BTZ+DEX
Started	10	3	8
Completed	4	2	5
Not completed	6	1	3
Adverse event, serious fatal	2	-	-
Physician decision	-	1	1
Consent withdrawn by subject	-	-	-
Death due to myeloma	2	-	-
Baseline sample unsuitable for analysis	-	-	1
Ineligible disease type	-	-	-
Lost to follow-up	-	-	1
Lack of efficacy	2	-	-

Number of subjects in period 1	Relapsed MM patients: LEN+DEX	Controls: Myeloproliferative disorders
Started	9	12
Completed	3	11
Not completed	6	1
Adverse event, serious fatal	2	-
Physician decision	1	-
Consent withdrawn by subject	1	-
Death due to myeloma	-	-
Baseline sample unsuitable for analysis	-	-
Ineligible disease type	-	1
Lost to follow-up	1	-
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	40	
From 65-84 years	0	0	
85 years and over	2	2	
Gender categorical			
Males and females.			
Units: Subjects			
Female	19	19	
Male	23	23	

End points

End points reporting groups

Reporting group title	Newly diagnosed MM patients: CTD
Reporting group description:	
Newly diagnosed MM patients treated with Cyclophosphamide Thalidomide & Dexamethasone. Treatment allocation NOT determined by study	
Reporting group title	Newly diagnosed MM patients: other
Reporting group description:	
Newly Diagnosed MM patients who were to receive treatment other than CTD. Treatment allocation NOT determined by study	
Reporting group title	Relapsed MM patients: BTZ+DEX
Reporting group description:	
Relapsed MM Patients to undergo Velcade & Dexamethasone. Treatment allocation NOT determined by study	
Reporting group title	Relapsed MM patients: LEN+DEX
Reporting group description:	
Relapsed MM Patients to undergo Lenalidomide & Dexamethasone. Treatment allocation NOT determined by study	
Reporting group title	Controls: Myeloproliferative disorders
Reporting group description:	
Patients with myeloproliferative disorders have a known propensity to develop thromboses (non treatment related) and will serve as the positive control group for this study. There are three major categories of myeloproliferative disorders: Chronic myelocytic leukemia, polycythemia rubra vera and myelofibrosis. These patients are followed up in a regular clinic in haematology outpatients. Based on the expected age and gender distribution of the experimental group ten of these control patients will be approached for consent in to the study. The same exclusion criteria (3.1.3) as for the experimental group will be adhered to. Treatment allocation NOT determined by study.	

Primary: To study the disruption of the endothelium, platelets and the coagulation cascade caused by the novel bio- chemotherapeutic combinations used for the treatment of multiple myeloma.

End point title	To study the disruption of the endothelium, platelets and the coagulation cascade caused by the novel bio- chemotherapeutic combinations used for the treatment of multiple myeloma.
End point description:	
End point type	Primary
End point timeframe:	
Baseline Day 8 of cycle 1 Day 1 of cycle 2 and 3 At end of chemotherapy course.	

End point values	Newly diagnosed MM patients: CTD	Newly diagnosed MM patients: other	Relapsed MM patients: BTZ+DEX	Relapsed MM patients: LEN+DEX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	3	8	9
Units: MV per microlitre	10	3	8	9

End point values	Controls: Myeloproliferative disorders			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: MV per microlitre	12			

Statistical analyses

Statistical analysis title	IBM SPSS
Comparison groups	Newly diagnosed MM patients: other v Relapsed MM patients: BTZ+DEX v Relapsed MM patients: LEN+DEX v Controls: Myeloproliferative disorders v Newly diagnosed MM patients: CTD
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 [1]
Method	IBM SPSS v20.0

Notes:

[1] - P values <0.05 were considered to be statistically significant.

Secondary: To correlate clinically evident thromboembolism (TE) with the type of treatment received and laboratory findings.

End point title	To correlate clinically evident thromboembolism (TE) with the type of treatment received and laboratory findings.

End point description:

Any thromboembolic event included arterial.

End point type	Secondary

End point timeframe:

Until 6 months after the last patient entered.

End point values	Newly diagnosed MM patients: CTD	Newly diagnosed MM patients: other	Relapsed MM patients: BTZ+DEX	Relapsed MM patients: LEN+DEX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	3	8	9
Units: Events	10	3	8	9

End point values	Controls: Myeloproliferative disorders			

Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Events	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From time of consent to last sample last patient.

Adverse event reporting additional description:

Bruising or superficial venous thrombosis or infection related to venesection.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Newly diagnosed MM patients: CTD

Reporting group description:

Newly diagnosed MM patients treated with Cyclophosphamide Thalidomide & Dexamethasone. Treatment allocation NOT determined by study

Serious adverse events	Newly diagnosed MM patients: CTD		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Newly diagnosed MM patients: CTD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no venesection related non-serious adverse events.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2012	Addition of standardised wording required by sponsor to comply with UK Trial Regulations and ICH/GCP
01 August 2013	Change to "Expected SAEs exempt from expedited notification" to include patients being treated on conventional standard of care protocols. Change to "Appendix B, Study arm/timepoint", point 5 now reads as soon as the first line chemotherapy course ends and before the second line course begins
16 February 2016	The amendment was submitted in order to discontinue the second consent. The initial proposal included the potential genomic study (DNA) from bone marrow or white cells of patients where a second consent was necessary. This part of the study has been superseded due to the inability to gain bone marrow samples.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated after the primary endpoint was reported as the frequency of VTE was very low to be able to produce a valid association of the study markers to frequency of VTE.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27566844