Clinical trial results:
An open label, multi-centre, randomised, parallel group phase II selection trial to identify the optimal starting dose of bendamustine (60 vs 100 mg/m2) when given in combination with thalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma

Summary

EudraCT number	2010-021451-12
Trial protocol	GB
Global end of trial date	11 April 2014

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	05 August 2015
Summary attachment (see zip file)	MUK01 End of Trial Report (MUKone End of Trial Report v1.0.pdf)

Trial information

Trial identification

Sponsor protocol code	HM10/9422

Additional study identifiers

ISRCTN number	ISRCTN90889843
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Hyde Terrace, Leeds, United Kingdom, LS2 9LN
Public contact	QA department, Leeds Institute of Clinical Trials Research, ctruq@leeds.ac.uk
Scientific contact	QA department, Leeds Institute of Clinical Trials Research, ctruq@leeds.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	09 July 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2013
Global end of trial reached?	Yes
Global end of trial date	11 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the optimum dose of bendamustine when combined with thalidomide and dexamethasone (BTD) in the treatment of relapsed/refractory multiple myeloma, based on response rates, tolerability, and progression-free survival (PFS).

Protection of trial subjects:

Patients will be monitored closely throughout the trial and will be asked to attend regular outpatient appointments.
Some visits will involve taking extra blood, urine and bone marrow samples. The additional samples will be taken at the same time as routine samples so will not involve additional needle punctures. Bone marrow tests are potentially painful. The potential side effects of the treatments used in this trial are explained within the patient information sheet. Treatment modifications will be made and supportive care given to minimise the side effects.

The frequency of the outpatient appointments during the follow up phase to monitor for disease progression will be
more than standard care. These visits will involve taking a blood and urine sample. Sites will endeavour to fast track
patients through clinics or day units where possible.

CTRU will prepare safety reports at least annually to the following: MHRA, main REC, Sponsor and the DMEC. All data will be anonymised. SAEs related to some of the IMPs will be shared with the relevant pharmaceutical company, who may pass this information outside the EEA. This is made explicit in the patient information sheet.

Trial data collected on paper will be sent to the CTRU and filed in locked filing cabinets. The CTRU reserve the option
of sharing anonymised data to evaluate safety, if required (eg. MHRA) and to develop new research including meta analysis.

Data is entered onto a trial database application, MACRO. The database is stored on a private network protected by a
firewall. Access to the database is restricted to trials staff by login and password.

The CTRU will comply with all aspects of Data Protection Act 1998. All information collected during the course of the
trial will be kept strictly confidential. All data collection forms, except consent forms, that are transferred to or from the
CTRU will be coded

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 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: 95
Worldwide total number of subjects	95
EEA total number of subjects	95

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)	51
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between January 2011 and July 2012 a total of 95 patients were entered into the MUK one trial. Recruitment was temporarily halted in September 2011 to allow the interim analysis to take place. As a result of this analysis all patients recruited from March 2012 were registered to receive 60mg/m2 Bendamustine with thalidomide and dexamethasone.

Pre-assignment

Screening details:

Patients will be approached during standard clinic visits for management of their disease and will be provided with verbal and written details about the trial. This will include detailed information about the rationale, design and personal implications of the trial.

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	B60TD 60mg/m2

Arm description:

60mg/m2 Bendamustine with thalidomide and
dexamethasone (B60TD) This was given over a 28 day cycle. Bendamustine given by IV on days 1 and 8,
thalidomide given orally continuously, dexamethasone given orally on days 1, 8, 15 and 22.
Treatment was given for a minimum of 6 cycles and up to 9 cycles, unless the treatment was not tolerated.

Arm type	Experimental
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

25mg bendamustine hydrochloride.

Reconstitute each vial of bendamustine containing 25mg bendamustine hydrochloride in 10 ml water for injection by shaking. The reconstituted concentrate contains 2.5mg bendamustine hydrochloride per ml and appears as a clear colourless solution.

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral 100mg/day Days 1 to 28. It is recommended that thalidomide is administered as a single dose at bedtime to reduce the impact of somnolence.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral 20mg/day Days 1, 8, 15, 22. It is recommended that dexamethasone is administered as a single dose in the morning.

Arm title	B100TD 100mg/m2

Arm description:

100mg/m2 Bendamustine with thalidomide and dexamethasone (B100TD). This was given over a 28 day cycle. Bendamustine given by IV on days 1 and 8, thalidomide given orally continuously, dexamethasone given orally on days 1, 8, 15 and 22. Treatment was given for a minimum of 6 cycles and up to 9 cycles, unless the treatment was not tolerated.

Arm type	Experimental
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Reconstitute each vial of bendamustine containing 100mg bendamustine hydrochloride in 40ml water for injection by shaking. The reconstituted concentrate contains 2.5mg bendamustine hydrochloride per ml and appears as a clear colourless solution.

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100mg/day Days 1 to 28, It is recommended that thalidomide is administered as a single dose at bedtime to reduce the impact of somnolence.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20mg/day Days 1, 8, 15, 22. It is recommended that dexamethasone is administered as a single dose in the morning.

Number of subjects in period 1[1]	B60TD 60mg/m2	B100TD 100mg/m2
Started	65	29
Completed	65	29

Notes:

[1] - 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 randomised to receive B60TD but the patient withdrew from the trial prior to starting treatment.

Baseline characteristics

Reporting groups	
Reporting group title	B60TD 60mg/m2
Reporting group description:	
60mg/m2 Bendamustine with thalidomide and dexamethasone (B60TD) This was given over a 28 day cycle. Bendamustine given by IV on days 1 and 8, thalidomide given orally continuously, dexamethasone given orally on days 1, 8, 15 and 22. Treatment was given for a minimum of 6 cycles and up to 9 cycles, unless the treatment was not tolerated.	
Reporting group title	B100TD 100mg/m2
Reporting group description:	
100mg/m2 Bendamustine with thalidomide and dexamethasone (B100TD). This was given over a 28 day cycle. Bendamustine given by IV on days 1 and 8, thalidomide given orally continuously, dexamethasone given orally on days 1, 8, 15 and 22. Treatment was given for a minimum of 6 cycles and up to 9 cycles, unless the treatment was not tolerated.	

Reporting group values	B60TD 60mg/m2	B100TD 100mg/m2	Total
Number of subjects	65	29	94
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 registration			
Units: years			
median	65	62	
full range (min-max)	34 to 82	50 to 79	-
Gender categorical Units: Subjects			
Female	29	16	45
Male	36	13	49

End points

End points reporting groups

Reporting group title	B60TD 60mg/m2

Reporting group description:

60mg/m2 Bendamustine with thalidomide and
dexamethasone (B60TD) This was given over a 28 day cycle. Bendamustine given by IV on days 1 and 8,
thalidomide given orally continuously, dexamethasone given orally on days 1, 8, 15 and 22.
Treatment was given for a minimum of 6 cycles and up to 9 cycles, unless the treatment was not tolerated.

Reporting group title	B100TD 100mg/m2

Reporting group description:

100mg/m2 Bendamustine with thalidomide and dexamethasone
(B100TD). This was given over a 28 day cycle. Bendamustine given by IV on days 1 and 8,
thalidomide given orally continuously, dexamethasone given orally on days 1, 8, 15 and 22.
Treatment was given for a minimum of 6 cycles and up to 9 cycles, unless the treatment was not tolerated.

Primary: The proportion of patients achieving at least a partial response

End point title	The proportion of patients achieving at least a partial

End point description:

This forms one of the joint primary endpoints of the trial: the proportion of patients achieving at least a partial response (as defined by the Modified International Working Group (IWG) Uniform Response Criteria) within six cycles of treatment, and the proportion of patients successfully able to receive both doses of their second cycle of bendamustine at full dose with no more than a 2 week delay.

The proportion of patients achieving at least a partial response is based on independently assessed response data.

End point type	Primary

End point timeframe:

within six cycles of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no formal comparison of the treatment arms. The trial was not designed to make any formal comparisons but to look at the arms independently, with focus on the lower limit of the 80% confidence intervals around the proportions. it has not been possible to add these values to the system as this is a countable outcome.

End point values	B60TD 60mg/m2	B100TD 100mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	29		
Units: Number of patients				
Achieved a partial response	27	8		
Did not achieve a partial response	38	21		

Statistical analyses

No statistical analyses for this end point

Primary: Progression-free survival at 12 months post-randomisation/registration

End point title	Progression-free survival at 12 months post-randomisation/registration[2]

End point description:

The primary endpoint of progression-free survival at 12 months post-randomisation/registration is used to allow treatment selection should both dosing schedules be determined sufficiently efficacious and tolerable.

End point type	Primary

End point timeframe:

12 months post-randomisation/registration.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: At the outset of the trial it was originally planned that the PFS endpoint would be used as a secondary selection criterion in the event that both B60TD and B100TD arms passed the activity and tolerability boundaries. Since the B100TD arm was closed to recruitment due to unacceptable tolerability this was not required.

End point values	B60TD 60mg/m2	B100TD 100mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	29		
Units: months				
median (confidence interval 95%)	6.5 (3.5 to 8)	2.4 (2 to 5.2)		

Statistical analyses

No statistical analyses for this end point

Primary: The proportion of patients successfully able to receive both doses of their second cycle of bendamustine at full dose with no more than a 2 week delay

End point title	The proportion of patients successfully able to receive both doses of their second cycle of bendamustine at full dose with no more than a 2 week delay[3]

End point description:

This forms on of the joint primary endpoints of the trial: the proportion of patients achieving at least a partial response (as defined by the Modified International Working Group (IWG) Uniform Response Criteria) within six cycles of treatment, and the proportion of patients successfully able to receive both doses of their second cycle of bendamustine at full dose with no more than a 2 week delay.

End point type	Primary

End point timeframe:

2 cycles of treatment

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no formal comparison of the treatment arms. The trial was not designed to make any formal comparisons but to look at the arms independently, with focus on the lower limit of the 80% confidence intervals around the proportions. it has not been possible to add these values to the system as this is a countable outcome.

End point values	B60TD 60mg/m2	B100TD 100mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[4]	29		
Units: Number of patients				
Tolerated therapy	36	15		
Did not tolerate therapy	27	14		

Notes:

[4] - Two patients were not assessable for tolerability.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum response rate

End point title	Maximum response rate

End point description:

Maximum response summaries are based on independently assessed response.

End point type	Secondary

End point timeframe:

Within 6 cycles of treatment

End point values	B60TD 60mg/m2	B100TD 100mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	29		
Units: number of patients				
sCR	0	0		
CR	1	1		
VGPR	2	1		
PR	24	6		
MR	9	3		
SD or NC	14	7		
PD	14	11		
Patient died before cycle 2	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients successfully receiving 6 cycles of treatment with no dose reductions or delays of more than 2 weeks

End point title	Proportion of patients successfully receiving 6 cycles of treatment with no dose reductions or delays of more than 2 weeks

End point description:

The proportion of patients successfully receiving six cycles of treatment with no dose reductions (with

the exception of day 8, cycle 1) or delays of more than 2 weeks

End point type	Secondary

End point timeframe:

6 cycles of treatment

End point values	B60TD 60mg/m2	B100TD 100mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	29		
Units: Number of patients				
Received 6 cycles, no reductions or delays	19	2		
Received < 6 cycles, reductions or delays	46	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Response duration

End point title	Response duration

End point description:

Response duration is defined as the time from date of achieving at least a PR within six cycles of treatment to the date of disease progression.

Patients who do not achieve at least a PR (including who have died without achieving a PR) are not included in this endpoint. Patients who achieve at least a PR and who die from causes other than disease progression are censored at the date of death. Patients who achieve at least a PR and who do not progress by the time of analysis will be censored at the last date they were known to be alive and progression free.

Response duration is based on locally assessed response therefore numbers of patients with at least a PR differ to those for the primary endpoint and maximum response summaries.

End point type	Secondary

End point timeframe:

From the date of achieving a partial response until the date of disease progression

End point values	B60TD 60mg/m2	B100TD 100mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	9		
Units: months				
median (confidence interval 95%)	7.95 (4.89 to 9.59)	5.86 (0.66 to 10.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next treatment

End point title	Time to next treatment

End point description:

Time to next treatment is defined as time from randomisation/registration to the date patient receives new treatment due to disease progression. Patients not receiving further treatment due to disease progression by the time of analysis will be censored at the last date known to be alive and not receiving further treatment. Patients who have died prior to receiving any further treatment will be censored at the date of death. Patients who receive further treatment but not due to disease progression will be censored at the date new treatment was received; if there are any cases where this information is not available patients will be censored at the last time they were known to have not received any new treatment.

End point type	Secondary

End point timeframe:

Time from registration to the date patient receives further treatment due to disease progression

End point values	B60TD 60mg/m2	B100TD 100mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	29		
Units: months				
median (confidence interval 95%)	10.55 (8.18 to 12.45)	8.02 (5.26 to 10.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: overall survival

End point title	overall survival

End point description:

Patients alive at the time of analysis will be censored at the last date known to be alive.
**NB the upper limit of the 95% confidence interval for median OS in the B60TD has been given as 99999 as the upper limit was not calculated due to the last patient being censored. This would ordinarily be set to '.', i.e. not calculated

End point type	Secondary

End point timeframe:

From date of randomisation/registration to date of death from any cause.

End point values	B60TD 60mg/m2	B100TD 100mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	29		
Units: months				
median (confidence interval 95%)	10.58 (8.18 to 99999)	12.19 (3.84 to 18.66)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse reactions will be collected for all patients from the time of start of protocol treatment until 30 days post cessation of trial therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	body system coding
Dictionary version	1

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

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: See attached End of Trial Report submitted to the MHRA in February 2015 for details of adverse events. Leeds Institute of Clinical Trials Research is an academic trials unit where full MedDRA coding is not the standard. It has therefore not been possible for adverse event data to be accurately entered into the full data view within EudraCT as all mandatory categories cannot be completed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2011	As part of the trial,patients will get the opportunity to take part in the King's College London Haemato-Oncology Tissue Bank Project (REC ref 08/H0906/94). Participation will be entirely optional and patients will be provided with a separate information sheet and consent form specific to the tissue bank. An additional stipulation that any brand of dexamethasone can be used in the trial in accordance with the protocol and section D2-2 in the EudraCT application form, that section D2-1 should not be completed.
18 July 2011	Exclusion criteria in the Protocol was updated to include: G-CSF is permitted for no more than 7 days prior to enrolment. Steroid treatment totalling greater than 160mg in the 14 days prior to enrolment. Additional indemnity statements were also included.
07 November 2011	Following a review by the DMEC the 100 mg arm of this study was closed and further recruitment temporarily suspended. The DMEC are currently reviewing further data from the 60 mg arm and will advise further
08 November 2011	The inclusion criteria was updated to include: Unsupported platelet count >75 x 109/L within 48 hours before enrolment (unless solely attributable to the myeloma in the opinion of the local investigator). Absolute neutrophil count >1.5 x109/L within 48 hours before enrolment (unless solely attributable to the myeloma in the opinion of the local investigator). G-CSF is permitted for no more than 7 days prior to enrolment. The exclusion criteria was updated to remove: Unsupported platelet count <75 x 10/9L within 14 days before enrolment (unless attributable solely to myeloma in the opinion of the local investigator) Absolute neutrophil count <105 x 109L within 14 days before enrolement. G-CSF is permitted for no more than 7 days prior to enrolment. Study definition of the protocol updated to include: ' If a patient is unable to receive both day 1 and day 8 of cycle 2 bendamustine at full dose, with no more than a 2 week delay, due to a low neutrophil count, this patient's data will be independently assessed to incorporate response assessments and all marker data in order to determine whether a low neutrophil count is likely due to disease or intolerability of bendamustine treatment. Only those patients for whom the independent review deems intolerability of bendamustine treatment will be classed as not able to tolerate treatment.' Primary Endpoint Analyses updated to include: An independent assessment of those patients unable to receive both day 1 and day 8 of cycle 2 bendamustine at full dose, with no more than a 2 week delay, due to a low neutrophil count, will be performed to incorporate response assessments and all marker data in order to determine whether a low neutrophil count is likely due to disease or intolerability of bendamustine treatment. The number of patients to which this applies, and the outcome of the independent assessment, will be summarized.

06 January 2012	Following a temporary suspension to the trial upon the advice of the DMEC and TSC the trial was reopened in the 60mg bendamustine arm only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 October 2011	Halt to recruitment following a review by the DMEC the 100mg arm of this study was closed and further recruitment suspended. The DMEC reviewed data from the 60mg arm and recruitment was reopened in the 60mg bendamustine arm only.	06 December 2011

Notes:

Limitations and caveats

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

The results presented are the ITT population only. The analysis was also performed for a per protocol population and study eligible population, as outlined in the attached end of trial report

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25891006