Clinical trial results:
A Randomised Study to Investigate the Efficacy of Bendamustine in Subjects with Indolent Non-Hodgkin's Lymphoma (NHL) Refractory to Rituximab

Summary

EudraCT number	2010-022102-41
Trial protocol	SK ES IT PT PL
Global end of trial date	31 July 2018

Results information

Result version number	v1 (current)
This version publication date	07 August 2019
First version publication date	07 August 2019

Trial information

Trial identification

Sponsor protocol code	BDM3502

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research Ltd.
Sponsor organisation address	194-198 Cambridge Science Park, Cambridge, United Kingdom, CB4 0AB
Public contact	Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.com
Scientific contact	Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.com

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	31 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2018
Global end of trial reached?	Yes
Global end of trial date	31 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to compare the efficacy of bendamustine against treatment of physician's choice (TPC) on progression free survival (PFS) in subjects with indolent B-cell in Non-Hodgkin's Lymphoma (NHL) that did not respond (stable disease [SD] or progressive disease [PD]) to rituximab or a rituximab containing regimen during or within 6 months of the previous rituximab treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Medications to treat nausea and vomiting or acquired infections during the study were allowed. Blood products and growth factors were allowed at the discretion of the Investigator.

Evidence for comparator:

Treatment in the reference arm was Treatment of Physician's Choice (TPC) which was defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was experimental in nature. The use of bendamustine was not permitted during the Treatment Phase.

Actual start date of recruitment	04 November 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	Poland: 3
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Australia: 91
Worldwide total number of subjects	109
EEA total number of subjects	18

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)	48
From 65 to 84 years	59
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 25 centers in 5 countries.

Pre-assignment

Screening details:

A total of 109 subjects were enrolled into this study, of which 21 subjects were screen failures (21 due to Non-compliance; 1 due to Subject's choice and 2 due to Other reason). Out of the 88 subjects randomised, 54 subjects completed and 31 subjects discontinued the study due to Adverse Events (21), Administrative (1) and Disease Progression (9).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bendamustine

Arm description:

Subjects received intravenously (IV) bendamustine 120 milligram per meter square (mg/m^2) on Days 1 and 2, every 21 days up to 6 cycles. However, if a subject was receiving clinical benefit after 6 cycles then a further 2 cycles of bendamustine were administered.

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

Dosage and administration details:

Subjects received intravenously bendamustine 120 mg/m^2

Arm title	Treatment of Physician’s Choice (TPC)

Arm description:

Subjects received treatment of physician’s choice which is defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was not experimental in nature. Bendamustine treatment was not permitted as TPC in the treatment phase.

Arm type	TPC
Investigational medicinal product name	Multiple cancer specific therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Variable treatment was given according to the label and based upon local institutional medical practice and clinical judgement.

Number of subjects in period 1[1]	Bendamustine	Treatment of Physician's Choice (TPC)
Started	58	30
Completed	39	15
Not completed	19	15
Never Treated	-	3
Administrative	1	-
Adverse event, non-fatal	14	7
Disease Progression	4	5

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: A total of 109 subjects were enrolled into this study, of which 21 subjects were screen failures and only 88 subjects randomized.

Baseline characteristics

Reporting groups	
Reporting group title	Bendamustine
Reporting group description:	
Subjects received intravenously (IV) bendamustine 120 milligram per meter square (mg/m^2) on Days 1 and 2, every 21 days up to 6 cycles. However, if a subject was receiving clinical benefit after 6 cycles then a further 2 cycles of bendamustine were administered.	
Reporting group title	Treatment of Physician's Choice (TPC)
Reporting group description:	
Subjects received treatment of physician's choice which is defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was not experimental in nature. Bendamustine treatment was not permitted as TPC in the treatment phase.	

Reporting group values	Bendamustine	Treatment of Physician's Choice (TPC)	Total
Number of subjects	58	30	88
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.8	65.4	
standard deviation	± 11.75	± 9.87	-
Gender categorical Units: Subjects			
Female	24	18	42
Male	34	12	46

End points

End points reporting groups

Reporting group title	Bendamustine
Reporting group description:	
Subjects received intravenously (IV) bendamustine 120 milligram per meter square (mg/m^2) on Days 1 and 2, every 21 days up to 6 cycles. However, if a subject was receiving clinical benefit after 6 cycles then a further 2 cycles of bendamustine were administered.	
Reporting group title	Treatment of Physician's Choice (TPC)
Reporting group description:	
Subjects received treatment of physician's choice which is defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was not experimental in nature. Bendamustine treatment was not permitted as TPC in the treatment phase.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
PFS is defined as time from randomization until disease progression or death due to any cause. For subjects who did not have an event (that is those who were lost to follow-up or who had not progressed at the date of data cut-off), PFS was censored. That is: PFS (days) = Date of progression/death/censoring – Date of randomization + 1. Subjects who did not progress in their disease were censored on the date of their last confirmed assessment. The Intent-to treat (ITT) population included all the subjects who were randomized irrespective of whether or not they actually received medication.	
End point type	Primary
End point timeframe:	
From Day 1 up to end of the study (Approximately up to 7.5 years); Follow up was done every 6 months and 3 months for subjects with and without disease progression respectively.	

End point values	Bendamustine	Treatment of Physician's Choice (TPC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	30		
Units: months				
median (confidence interval 95%)	18.5 (10.2 to 27.2)	11.2 (7.1 to 18.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bendamustine v Treatment of Physician's Choice (TPC)

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.297
Method	Log-Rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.752
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.403
upper limit	1.403

Secondary: Percentage of Subjects with Overall Response Rate (ORR)

End point title	Percentage of Subjects with Overall Response Rate (ORR)

End point description:

ORR is defined as Percentage of subjects who confirmed Complete Remission (CR) or Partial Remission (PR) called as responders. Non-responders included subjects with stable disease (SD) or progressive disease (PD). CR is defined as complete disappearance of all detectable clinical evidence of disease and disease related symptoms if present before therapy; all lymph nodes and nodal masses must have regressed on computed tomography (CT) to normal size (less than or equal to [<=] 1.5 centimeter [cm] in their greatest transverse diameter for nodes greater than [>] 1.5 cm before therapy). PR is defined as least a 50% decrease in the sum of product of the diameters (SPD) of up to six of largest dominant nodes or nodal masses. A subject was considered to have SD when he or she failed to attain the criteria needed for a CR or PR, but did not fulfill those for PD. The ITT population comprised of all subjects who were randomised irrespective of whether or not they actually received medication.

End point type	Secondary

End point timeframe:

From Day 1 up to end of the study (Approximately up to 7.5 years)

End point values	Bendamustine	Treatment of Physician's Choice (TPC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	30		
Units: Percentage of subjects				
number (not applicable)				
ORR	77.6	56.7		
CR	25.9	10.0		
PR	51.7	46.7		
SD	12.1	20.0		
PD	1.7	13.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR is defined as time from initial response (CR/PR) to progression or death. Where CR is defined as complete disappearance of all detectable clinical evidence of disease and disease related symptoms if present before therapy; all lymph nodes and nodal masses must have regressed on CT to normal size (<= 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). PR is defined as least a 50% decrease in the sum of product of the diameters of up to six of largest dominant nodes or nodal masses. A subject was considered to have SD when he or she failed to attain the criteria needed for a CR or PR, but did not fulfill those for PD. The ITT population comprised of all subjects who were randomised irrespective of whether or not they actually received medication. Here '99999' signifies not estimable as upper bound not reached.

End point type	Secondary

End point timeframe:

From Day 1 up to end of the study (Approximately up to 7.5 years)

End point values	Bendamustine	Treatment of Physician's Choice (TPC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	30		
Units: months				
median (confidence interval 95%)	17.5 (8.0 to 21.2)	10.2 (5.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as time from randomization to death. The ITT population comprised of all subjects who were randomized irrespective of whether or not they actually received medication. Here '99999' in median signifies not estimable median survival time cannot be estimated because this group did not reached at the analysis cut off (survival was greater than 50% in the TPC group at the time of the last analysis), while '99999' in upper bound signifies not estimable as upper bound not reached.

End point type	Secondary

End point timeframe:

From Day 1 up to end of the study (Approximately up to 7.5 years)

End point values	Bendamustine	Treatment of Physician's Choice (TPC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	30		
Units: months				
median (confidence interval 95%)	38.4 (23.3 to	99999 (19.6 to		

99999)	99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs) and Serious Treatment Emergent Adverse Events

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs) and Serious Treatment Emergent Adverse Events

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, including placebo, and which did not necessarily have to have had a causal relationship with treatment. An SAE is any untoward medical occurrence that at any dose that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect. TEAEs are defined as new or worsening adverse events with an onset date occurring on or after first dose date of study medication inclusive to 30 days post-last dose. The Safety Population included all subjects who were randomized and who received at least 1 dose of study treatment. Here, 'Number of subjects analysed' signifies the subjects evaluable for this population.

End point type	Secondary

End point timeframe:

From Day 1 of treatment administration up to 30 days after last treatment

End point values	Bendamustine	Treatment of Physician's Choice (TPC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	27		
Units: Subjects				
TEAE	58	27		
TEAE of CTC grade 3 or 4	44	18		
Serious TEAE	27	7		
TEAE Leading to Death	1	0		
TEAE Leading to Discontinuation of study drug	13	3		
TEAE Leading to Dose Reduction	20	6		
TEAE Leading to Dose Withheld	32	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Health Related Quality of Life (HRQL) as Assessed by EuroQol Group (EQ-5D)

End point title	Change from Baseline in Health Related Quality of Life (HRQL) as Assessed by EuroQol Group (EQ-5D)

End point description:

EQ-5D is an instrument for measuring health outcome and consists of five dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression and a visual analog scale (VAS). Each dimension has 3 levels: No problems, Some problems, Severe problems. Responses to the single dimensions will be coded numerically 1 to 3 in order of decreasing health status. Responses to the EQ-5D will be converted into an EQ-5D index, which provides a single summary by weighting the response levels in each dimension . The weighted index constitutes a measure of utility and represents a health state from 0 to 1, where 1 is fullest health. This index will be derived only from patients who have provided a complete 5- response profile. The EQ VAS records the subject's self–rated health where the endpoints are worst imaginable health (score=0) to best imaginable health (score =100). Here 'n' signifies number of subjects analysed for category at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 63 and Day 126

End point values	Bendamustine	Treatment of Physician's Choice (TPC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	30		
Units: Units on a scale				
least squares mean (standard error)				
Day 63: EQ-5D Index (n=44, 17)	0.748 (± 0.0358)	0.761 (± 0.0552)		
Day 126: EQ-5D Index (n=29, 9)	0.738 (± 0.0305)	0.847 (± 0.0511)		
Day 63: EQ-5D VAS (n= 44, 17)	62.5 (± 2.91)	58.5 (± 4.50)		
Day 126: EQ-5D VAS (n=28, 9)	60.9 (± 3.81)	63.2 (± 6.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Health Related Quality of Life as Assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Version 3.0

End point title	Change from Baseline in Health Related Quality of Life as Assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Version 3.0

End point description:

EORTC QLQ-C30 v3 is composed of 2 multi-item scales and single-item measures,: 1) Global scale: health status/quality of life (QoL) 2) Functional scales: physical/role/emotional/cognitive/social; 3) Symptom scales: fatigue/nausea/vomiting/pain/dyspnoea/insomnia/appetite loss/constipation/diarrhoea/financial impact. Global health status/ QoL questions are rated from very poor - excellent on scale of 1-7. All other questions are rated as not at all/a little/quite a bit/very much, coded from 1-4 in decreasing order health status. Each multi-item scales includes a different set of items - with no item repetition. All scales are transformed to have scores ranging from 0-100. High score for functional scale represents high/healthy functioning level, high score for global health status /QoL represents high QoL but high score for a symptom scale/item represents a high level of symptomatology/ problem. Here 'n' signifies number of subjects analysed for category at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 63 and Day 126

End point values	Bendamustine	Treatment of Physician's Choice (TPC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	30		
Units: Units on a scale				
least squares mean (standard error)				
Day 63: Global health status/QoL (n= 44, 17)	56.73 (± 3.569)	58.69 (± 5.610)		
Day 126: Global health status/QoL (n= 29, 9)	55.68 (± 3.894)	64.31 (± 6.558)		
Day 63: Physical functioning (n= 45, 17)	67.13 (± 3.427)	70.14 (± 5.401)		
Day 126: Physical functioning (n= 30, 9)	68.1 (± 3.449)	83.58 (± 5.866)		
Day 63: Role functioning (n= 45, 17)	59.55 (± 4.875)	62.26 (± 7.683)		
Day 126: Role functioning (n= 30, 9)	55.73 (± 5.461)	77.24 (± 9.268)		
Day 63: Emotional functioning (n= 45, 17)	75.42 (± 2.715)	78.06 (± 4.285)		
Day 126: Emotional functioning (n= 30, 9)	80.80 (± 3.340)	77.01 (± 5.690)		
Day 63: Cognitive functioning (n= 45, 17)	74.03 (± 3.501)	78.53 (± 5.518)		
Day 126: Cognitive functioning (n= 30, 9)	77.77 (± 4.112)	85.58 (± 7.023)		
Day 63: Social functioning (n= 44, 17)	61.90 (± 4.787)	63.61 (± 7.773)		
Day 126: Social functioning (n= 30, 9)	66.28 (± 5.108)	79.83 (± 9.291)		
Day 63: Fatigue (n= 45, 17)	51.09 (± 4.294)	39.86 (± 6.770)		
Day 126: Fatigue (n= 30, 9)	50.61 (± 4.389)	26.09 (± 7.487)		
Day 63: Nausea and vomiting (n= 45, 17)	17.61 (± 2.471)	10.92 (± 3.893)		
Day 126: Nausea and vomiting (n= 30, 9)	8.63 (± 3.005)	5.13 (± 5.094)		
Day 63: Pain (n= 45, 17)	21.89 (± 3.834)	25.24 (± 6.087)		
Day 126: Pain (n= 30, 9)	14.06 (± 4.322)	15.4 (± 7.429)		
Day 63: Dyspnoea (n= 45, 17)	22.01 (± 3.676)	14.09 (± 5.816)		
Day 126: Dyspnoea (n= 30, 9)	25.68 (± 4.689)	7.79 (± 7.991)		
Day 63: Insomnia (n= 45, 17)	33.51 (± 3.996)	41.10 (± 6.299)		
Day 126: Insomnia (n= 30, 9)	38.49 (± 6.813)	26.63 (± 11.571)		
Day 63: Appetite loss (n= 45, 17)	30.51 (± 4.398)	27.36 (± 6.936)		

Day 126: Appetite loss (n= 30, 9)	27.51 (± 5.24)	11.59 (± 9.057)		
Day 63: Constipation (n= 45, 17)	29.58 (± 3.671)	20.67 (± 5.797)		
Day 126: Constipation (n= 30, 9)	11.12 (± 3.523)	7.04 (± 5.971)		
Day 63: Diarrhoea (n= 45, 17)	17.75 (± 3.680)	7.20 (± 5.791)		
Day 126: Diarrhoea (n= 30, 9)	12.6 (± 3.893)	8.24 (± 6.591)		
Day 63: Financial difficulties (n= 44, 17)	21.21 (± 3.173)	23.59 (± 4.988)		
Day 126: Financial difficulties (n= 30, 9)	18.89 (± 4.068)	32.07 (± 6.867)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 of treatment administration up to 30 days after last treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Bendamustine

Reporting group description:

Subjects received intravenously (IV) bendamustine 120 milligram per meter square (mg/m^2) on Days 1 and 2, every 21 days up to 6 cycles. However, if a subject was receiving clinical benefit after 6 cycles then a further 2 cycles of bendamustine were administered.

Reporting group title	Treatment of Physician's Choice (TPC)

Reporting group description:

Subjects received treatment of physician's choice which is defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was not experimental in nature. Bendamustine treatment was not permitted as TPC in the treatment phase.

Serious adverse events	Bendamustine	Treatment of Physician's Choice (TPC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 58 (46.55%)	7 / 27 (25.93%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 58 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 58 (1.72%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 58 (17.24%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	7 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 58 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 58 (8.62%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	3 / 58 (5.17%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			

subjects affected / exposed	0 / 58 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			

subjects affected / exposed	1 / 58 (1.72%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bendamustine	Treatment of Physician's Choice (TPC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 58 (100.00%)	27 / 27 (100.00%)	
Investigations			
Platelet count decreased			
subjects affected / exposed	10 / 58 (17.24%)	3 / 27 (11.11%)	
occurrences (all)	23	7	
Neutrophil count decreased			
subjects affected / exposed	11 / 58 (18.97%)	1 / 27 (3.70%)	
occurrences (all)	34	1	
Weight decreased			
subjects affected / exposed	6 / 58 (10.34%)	1 / 27 (3.70%)	
occurrences (all)	8	1	
White blood cell count decreased			
subjects affected / exposed	5 / 58 (8.62%)	2 / 27 (7.41%)	
occurrences (all)	13	4	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 58 (1.72%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 58 (12.07%)	2 / 27 (7.41%)	
occurrences (all)	8	3	
Dysgeusia			
subjects affected / exposed	6 / 58 (10.34%)	1 / 27 (3.70%)	
occurrences (all)	6	1	
Lethargy			
subjects affected / exposed	4 / 58 (6.90%)	3 / 27 (11.11%)	
occurrences (all)	5	3	

Neuropathy peripheral			
subjects affected / exposed	4 / 58 (6.90%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
Dizziness			
subjects affected / exposed	3 / 58 (5.17%)	0 / 27 (0.00%)	
occurrences (all)	5	0	
Presyncope			
subjects affected / exposed	3 / 58 (5.17%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	27 / 58 (46.55%)	8 / 27 (29.63%)	
occurrences (all)	40	10	
Pyrexia			
subjects affected / exposed	5 / 58 (8.62%)	2 / 27 (7.41%)	
occurrences (all)	15	2	
Oedema peripheral			
subjects affected / exposed	8 / 58 (13.79%)	1 / 27 (3.70%)	
occurrences (all)	9	2	
Asthenia			
subjects affected / exposed	7 / 58 (12.07%)	0 / 27 (0.00%)	
occurrences (all)	10	0	
Chills			
subjects affected / exposed	5 / 58 (8.62%)	0 / 27 (0.00%)	
occurrences (all)	7	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	19 / 58 (32.76%)	8 / 27 (29.63%)	
occurrences (all)	45	13	
Anaemia			
subjects affected / exposed	13 / 58 (22.41%)	5 / 27 (18.52%)	
occurrences (all)	31	12	
Thrombocytopenia			
subjects affected / exposed	13 / 58 (22.41%)	4 / 27 (14.81%)	
occurrences (all)	36	6	
Leukopenia			

subjects affected / exposed	0 / 58 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	33 / 58 (56.90%)	9 / 27 (33.33%)	
occurrences (all)	50	9	
Constipation			
subjects affected / exposed	27 / 58 (46.55%)	4 / 27 (14.81%)	
occurrences (all)	31	4	
Diarrhoea			
subjects affected / exposed	18 / 58 (31.03%)	5 / 27 (18.52%)	
occurrences (all)	29	7	
Vomiting			
subjects affected / exposed	14 / 58 (24.14%)	5 / 27 (18.52%)	
occurrences (all)	22	5	
Mouth ulceration			
subjects affected / exposed	9 / 58 (15.52%)	1 / 27 (3.70%)	
occurrences (all)	10	1	
Abdominal pain			
subjects affected / exposed	4 / 58 (6.90%)	2 / 27 (7.41%)	
occurrences (all)	5	2	
Dry mouth			
subjects affected / exposed	5 / 58 (8.62%)	1 / 27 (3.70%)	
occurrences (all)	6	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 58 (10.34%)	0 / 27 (0.00%)	
occurrences (all)	6	0	
Abdominal pain upper			
subjects affected / exposed	3 / 58 (5.17%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Stomatitis			
subjects affected / exposed	3 / 58 (5.17%)	2 / 27 (7.41%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	12 / 58 (20.69%)	5 / 27 (18.52%)	
occurrences (all)	15	7	
Dyspnoea			
subjects affected / exposed	7 / 58 (12.07%)	0 / 27 (0.00%)	
occurrences (all)	8	0	
Rhinitis allergic			
subjects affected / exposed	3 / 58 (5.17%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Oropharyngeal pain			
subjects affected / exposed	3 / 58 (5.17%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 58 (12.07%)	2 / 27 (7.41%)	
occurrences (all)	8	2	
Dry skin			
subjects affected / exposed	5 / 58 (8.62%)	1 / 27 (3.70%)	
occurrences (all)	5	1	
Pruritus			
subjects affected / exposed	3 / 58 (5.17%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 58 (8.62%)	2 / 27 (7.41%)	
occurrences (all)	5	2	
Anxiety			
subjects affected / exposed	3 / 58 (5.17%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
Depression			
subjects affected / exposed	1 / 58 (1.72%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	7 / 58 (12.07%)	1 / 27 (3.70%)	
occurrences (all)	7	2	

Musculoskeletal pain			
subjects affected / exposed	2 / 58 (3.45%)	1 / 27 (3.70%)	
occurrences (all)	6	1	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	8 / 58 (13.79%)	0 / 27 (0.00%)	
occurrences (all)	8	0	
Urinary tract infection			
subjects affected / exposed	3 / 58 (5.17%)	2 / 27 (7.41%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 58 (24.14%)	3 / 27 (11.11%)	
occurrences (all)	16	3	
Hypokalaemia			
subjects affected / exposed	8 / 58 (13.79%)	2 / 27 (7.41%)	
occurrences (all)	12	2	
Hypomagnesaemia			
subjects affected / exposed	6 / 58 (10.34%)	1 / 27 (3.70%)	
occurrences (all)	7	1	
Hypoalbuminaemia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 27 (0.00%)	
occurrences (all)	6	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2011	The overall reason of this amendment was to update study design methodology.

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 did not achieve the recruitment goal and was therefore terminated early.

Notes: