Clinical trial results:
Bortezomib (Velcade®): a feasibility and phase II study in childhood relapsed acute lymphoblastic leukemia

Summary

EudraCT number	2009-014037-25
Trial protocol	NL DE IT BE DK AT
Global end of trial date	21 October 2014

Results information

Result version number	v1 (current)
This version publication date	21 March 2018
First version publication date	21 March 2018
Summary attachment (see zip file)	Summary Bortezomib_CSR (CSR Bortezomib dd 23-05-2017-summary.pdf)

Trial information

Trial identification

Sponsor protocol code	ITCC021

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Erasmus MC
Sponsor organisation address	Dr. Molenwaterplein 60, Rotterdam, Netherlands, 3015 GD
Public contact	C.M. Zwaan, Erasmus MC, 0031 107036691, c.m.zwaan@erasmusmc.nl
Scientific contact	C.M. Zwaan, Erasmus MC, 0031 107036691, c.m.zwaan@erasmusmc.nl

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	23 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2014
Global end of trial reached?	Yes
Global end of trial date	21 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the antileukemic activity of combination chemotherapy including bortezomib as reinduction therapy in childhood relapsed/refractory ALL

Protection of trial subjects:

By the Informed consent and voluntary participation in the trial.
Surgical interventions take place under anaesthesia.

Background therapy:

Dexamethasone, vincristine and intrathecal methotrexate

Evidence for comparator:

All patients will be treated with one cycle of bortezomib, consisting of 4 doses in 2 weeks.
However, they will be randomised 1:1 in 2 arms, group A getting"early" bortezomib, starting at day 1 of therapy, and group B getting
"late" bortezomib, starting at day 8.
Randomization will be stratified for the number of circulating leukemic blasts at inclusion in this study protocol. This design allows demonstrating an additional antileukemic
effect of bortezomib when added to dexamethasone, after 1 week of therapy, measured by a reduction in ALL cells in peripheral blood and bone marrow. In addition, this design allows comparing the toxicity of limited (group A) and more extended (group B) overlap of administrations of bortezomib and vincristine.

Actual start date of recruitment	08 October 2010
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	Netherlands: 9
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	France: 6
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	4
Children (2-11 years)	14
Adolescents (12-17 years)	11
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study initiation date / first subject visit: October 8, 2010
Study completion date / last subject completed: October 21, 2014
29 subjects enrolled; 29 subjects completed and analyzed.

Pre-assignment

Screening details:

Screening measures conducted prior to enrollment constitute a standard battery of tests designed to thoroughly examine the potential subject for any medical issues.

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	Arm A

Arm description:

Arm A received bortezomib on days 1, 4, 8 and 11

Arm type	Active comparator
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per day, 1.3 mg/m2 milligram(s)/square meter

Arm title	Arm B

Arm description:

Arm B received bortezomib on days 8, 11, 15 and 18

Arm type	Active comparator
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per day, 1.3 mg/m2 milligram(s)/square meter

Number of subjects in period 1	Arm A	Arm B
Started	14	15
Completed	14	15

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	29	29	
Age categorical			
Age at randomization (years)			
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)	4	4	
Children (2-11 years)	14	14	
Adolescents (12-17 years)	11	11	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age at randomization (years)			
Units: years			
median	9.8		
full range (min-max)	1 to 17	-	
Gender categorical			
Units: Subjects			
Female	12	12	
Male	17	17	
Relapse type			
Units: Subjects			
2nd/subs relapsed ALL	16	16	
1st relapsed ALL after allo-SCT	11	11	
Refractory 1st relapsed ALL	2	2	
Immunophenotype			
Units: Subjects			
T-ALL	4	4	
Pro-B ALL	7	7	
Pre-B ALL	8	8	
Common-ALL	10	10	

Subject analysis sets

Subject analysis set title	Full analysis
Subject analysis set type	Full analysis

Subject analysis set description:

29 patients with information on response and/or toxicity after cycle 1 enrolled in this study. It coincides

with the safety analysis set

Subject analysis set title	Full Analysis Set Primary Efficacy
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set Primary Efficacy (FAS Primary Efficacy), which included all randomized patients who had a valid absolute PB blast count measurement at day 8 of treatment. This set was used for the primary analysis.

Subject analysis set title	Per Protocol Analysis Set Primary Efficacy
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Analysis Set Primary Efficacy (PPS Primary Efficacy), which was used for the primary analysis, and included all patients in the FAS Primary Efficacy who completed the study and did not have any major protocol deviations.

Subject analysis set title	Full Analysis Set Secondary Efficacy, BM day 8
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set Secondary Efficacy (FAS Secondary Efficacy), which was used for the analysis of secondary efficacy objectives and, for each endpoint, included all patients who had a valid measurement.

Subject analysis set title	Full Analysis Set Secondary Efficacy, BM day 22
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set Secondary Efficacy (FAS Secondary Efficacy), which was used for the analysis of secondary efficacy objectives and, for each endpoint, included all patients who had a valid measurement.

Subject analysis set title	Full Analysis Set Secondary Efficacy, PB day 22
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set Secondary Efficacy (FAS Secondary Efficacy), which was used for the analysis of secondary efficacy objectives and, for each endpoint, included all patients who had a valid measurement.

Subject analysis set title	Full analysis set secondary efficacy, day 43
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set Secondary Efficacy (FAS Secondary Efficacy), which was used for the analysis of secondary efficacy objectives and, for each endpoint, included all patients who had a valid measurement.

Reporting group values	Full analysis	Full Analysis Set Primary Efficacy	Per Protocol Analysis Set Primary Efficacy
Number of subjects	29	26	24
Age categorical			
Age at randomization (years)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	4	3	2
Children (2-11 years)	14	12	12
Adolescents (12-17 years)	11	11	10
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0

Age continuous			
Age at randomization (years)			
Units: years			
median	9.8	10.2	10.2
full range (min-max)	1 to 17	1 to 17	1 to 17
Gender categorical			
Units: Subjects			
Female	12	12	12
Male	17	14	12
Relapse type			
Units: Subjects			
2nd/subs relapsed ALL	16	15	14
1st relapsed ALL after allo-SCT	11	9	8
Refractory 1st relapsed ALL	2	2	2
Immunophenotype			
Units: Subjects			
T-ALL	4	4	4
Pro-B ALL	7	6	5
Pre-B ALL	8	7	6
Common-ALL	10	9	9

Reporting group values	Full Analysis Set Secondary Efficacy, BM day 8	Full Analysis Set Secondary Efficacy, BM day 22	Full Analysis Set Secondary Efficacy, PB day 22
Number of subjects	27	24	19
Age categorical			
Age at randomization (years)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	3	3	2
Children (2-11 years)	13	11	9
Adolescents (12-17 years)	11	10	8
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at randomization (years)			
Units: years			
median	10.0	9.9	9.8
full range (min-max)	1 to 17	1 to 17	1 to 17
Gender categorical			
Units: Subjects			
Female	12	10	6
Male	15	14	13
Relapse type			
Units: Subjects			
2nd/subs relapsed ALL	16	13	9
1st relapsed ALL after allo-SCT	9	9	10
Refractory 1st relapsed ALL	2	2	0

Immunophenotype Units: Subjects			
T-ALL	4	4	4
Pro-B ALL	6	6	5
Pre-B ALL	8	8	4
Common-ALL	9	6	6

Reporting group values	Full analysis set secondary efficacy, day 43		
Number of subjects	8		
Age categorical			
Age at randomization (years)			
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)	1		
Children (2-11 years)	3		
Adolescents (12-17 years)	4		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Age at randomization (years)			
Units: years			
median	12.4		
full range (min-max)	1 to 16		
Gender categorical Units: Subjects			
Female	4		
Male	4		
Relapse type Units: Subjects			
2nd/subs relapsed ALL	3		
1st relapsed ALL after allo-SCT	5		
Refractory 1st relapsed ALL	0		
Immunophenotype Units: Subjects			
T-ALL	1		
Pro-B ALL	4		
Pre-B ALL	2		
Common-ALL	1		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Arm A received bortezomib on days 1, 4, 8 and 11	
Reporting group title	Arm B
Reporting group description:	
Arm B received bortezomib on days 8, 11, 15 and 18	
Subject analysis set title	Full analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
29 patients with information on response and/or toxicity after cycle 1 enrolled in this study. It coincides with the safety analysis set	
Subject analysis set title	Full Analysis Set Primary Efficacy
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set Primary Efficacy (FAS Primary Efficacy), which included all randomized patients who had a valid absolute PB blast count measurement at day 8 of treatment. This set was used for the primary analysis.	
Subject analysis set title	Per Protocol Analysis Set Primary Efficacy
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Analysis Set Primary Efficacy (PPS Primary Efficacy), which was used for the primary analysis, and included all patients in the FAS Primary Efficacy who completed the study and did not have any major protocol deviations.	
Subject analysis set title	Full Analysis Set Secondary Efficacy, BM day 8
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set Secondary Efficacy (FAS Secondary Efficacy), which was used for the analysis of secondary efficacy objectives and, for each endpoint, included all patients who had a valid measurement.	
Subject analysis set title	Full Analysis Set Secondary Efficacy, BM day 22
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set Secondary Efficacy (FAS Secondary Efficacy), which was used for the analysis of secondary efficacy objectives and, for each endpoint, included all patients who had a valid measurement.	
Subject analysis set title	Full Analysis Set Secondary Efficacy, PB day 22
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set Secondary Efficacy (FAS Secondary Efficacy), which was used for the analysis of secondary efficacy objectives and, for each endpoint, included all patients who had a valid measurement.	
Subject analysis set title	Full analysis set secondary efficacy, day 43
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set Secondary Efficacy (FAS Secondary Efficacy), which was used for the analysis of secondary efficacy objectives and, for each endpoint, included all patients who had a valid measurement.	

Primary: Antileukemic activity of bortezomib when added to dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute peripheral blood (PB) blast count on day 8 of treatment.

End point title	Antileukemic activity of bortezomib when added to dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute peripheral blood (PB) blast count on day 8 of treatment.

End point description:

End point type	Primary

End point timeframe:

Day 8 of treatment

End point values	Arm A	Arm B	Full Analysis Set Primary Efficacy	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	14	26	
Units: Absolute blast count per microliter				
median (full range (min-max))	465 (2 to 38888)	774 (4 to 203820)	732 (2 to 203820)	

Attachments (see zip file)	Absolute blast count, day 8 (full analysis set)/pbc_d8_fas.bmp

Statistical analyses

Statistical analysis title	Mann-Whitney U test PB day 8, full analysis set
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Location shift (BTZ early-BTZ late)
Point estimate	-177.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3638
upper limit	630
Variability estimate	Standard error of the mean
Dispersion value	1100.02

Secondary: Antileukemic activity of bortezomib when added to dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute bone

marrow (BM) blast percentage on day 8 of treatment	
End point title	Antileukemic activity of bortezomib when added to dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute bone marrow (BM) blast percentage on day 8 of treatment
End point description:	
End point type	Secondary
End point timeframe: Day 8 of treatment	

End point values	Arm A	Arm B	Full Analysis Set Secondary Efficacy, BM day 8	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	14	27	
Units: blast percentage				
median (full range (min-max))	86 (3 to 99)	79 (1 to 96)	84 (1 to 99)	

Attachments (see zip file)	Absolute BM blast percentage, day 8/bm_d8_fas.bmp

Statistical analyses

Statistical analysis title	Mann-Whitney U test BM day 8, full analysis set
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Location shift (BTZ early-BTZ late)
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	24
Variability estimate	Standard error of the mean
Dispersion value	7.7808

Secondary: Antileukemic activity of bortezomib when added to dematha sone and vincristine and intrathecal methotrexate, as determined by the absolute bone marrow (BM) blast percentage on day 22 of treatment	
End point title	Antileukemic activity of bortezomib when added to

	dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute bone marrow (BM) blast percentage on day 22 of treatment

End point description:

End point type	Secondary

End point timeframe:

Day 22 of treatment

End point values	Arm A	Arm B	Full Analysis Set Secondary Efficacy, BM day 22	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	13	24	
Units: blast percentage				
median (full range (min-max))	13 (0 to 95)	12 (0 to 98)	12.5 (0 to 98)	

Attachments (see zip file)	Absolute BM blast percentage, day 22/bm_d22_fas.bmp

Statistical analyses

Statistical analysis title	Mann-Whitney U test BM day 22, full analysis set
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Location shift (BTZ early-BTZ late)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	59
Variability estimate	Standard error of the mean
Dispersion value	19.6432

Secondary: Antileukemic activity of bortezomib when added to dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute peripheral blood (PB) blast count on day 22 of treatment

End point title	Antileukemic activity of bortezomib when added to dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute peripheral blood (PB) blast count on day 22 of treatment

End point description:

End point type	Secondary
End point timeframe:	
Day 22 of treatment	

End point values	Arm A	Arm B	Full Analysis Set Secondary Efficacy, PB day 22	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	8	11	19	
Units: Absolute blast count per microliter				
median (full range (min-max))	0 (0 to 265)	7 (0 to 33288)	0 (0 to 33288)	

Statistical analyses

Statistical analysis title	Mann-Whitney U test PB day 22, full analysis set
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Location shift (BTZ early-BTZ late)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-130
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	39.7966

Secondary: Feasibility of combining bortezomib with dexamethasone and vincristine and intrathecal methotrexate

End point title	Feasibility of combining bortezomib with dexamethasone and vincristine and intrathecal methotrexate

End point description:

Feasibility of combining bortezomib with dexamethasone and vincristine and intrathecal methotrexate, as determined by the percentage of patients in whom bortezomib had to be dose reduced or withdrawn because of toxicity.

End point type	Secondary
End point timeframe:	
All study	

End point values	Arm A	Arm B	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	15	29	
Units: Number of patients				
Dose-reduced/withdrawn at any cycle	2	3	5	
Not dose-reduced/withdrawn	12	12	24	

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity of bortezomib when combined with dexamethasone and vincristine and intrathecal methotrexate, as determined by the percentage of patients suffering from grade III/IV toxicity in any field

End point title	Toxicity of bortezomib when combined with dexamethasone and vincristine and intrathecal methotrexate, as determined by the percentage of patients suffering from grade III/IV toxicity in any field

End point description:

End point type	Secondary

End point timeframe:

All study

End point values	Arm A	Arm B	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	15	29	
Units: Number of patients				
>= grade III/IV toxicity	14	15	29	
< grade III/IV toxicity	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Feasibility of combining a second cycle of bortezomib with combination chemotherapy, its toxicity and antileukemic activity, day 43

End point title	Feasibility of combining a second cycle of bortezomib with combination chemotherapy, its toxicity and antileukemic activity, day 43

End point description:

Determine the feasibility of combining a second cycle of bortezomib with combination chemotherapy, its toxicity and antileukemic activity, as measured after 6 weeks of therapy by bone marrow, peripheral blood and cerebrospinal fluid

End point type	Secondary

End point timeframe:

Day 43 of treatment

End point values	Arm A	Arm B	Full analysis set secondary efficacy, day 43	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	5	8	
Units: Blast percentage				
median (full range (min-max))	0 (0 to 0)	1 (0 to 15)	0 (0 to 15)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs will be collected until 30 days after the administration of the last dose of bortezomib.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	3

Reporting groups	
Reporting group title	Arm A (early bortezomib)
Reporting group description: -	
Reporting group title	Arm B (late bortezomib)
Reporting group description: -	

Serious adverse events	Arm A (early bortezomib)	Arm B (late bortezomib)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 14 (42.86%)	4 / 15 (26.67%)	
number of deaths (all causes)	11	13	
number of deaths resulting from adverse events	5	2	
Nervous system disorders			
Hemorrhage, CNS			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neuropathic pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Blood/bone marrow other, progression of leukemia			

subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Febrile neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death, multi-organ failure			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death (sudden/NOS)			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Psychosis (hallucinations)			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Skin infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infection with grade 3 or 4 neutrophils			

subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Infection with neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Arm A (early bortezomib)	Arm B (late bortezomib)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	15 / 15 (100.00%)	
Investigations			
ALAT			
subjects affected / exposed	3 / 14 (21.43%)	1 / 15 (6.67%)	
occurrences (all)	5	2	
ALT increase			
subjects affected / exposed	1 / 14 (7.14%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
ALT/GPT transaminase			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
AST increase			
subjects affected / exposed	1 / 14 (7.14%)	2 / 15 (13.33%)	
occurrences (all)	1	4	
GGT increase			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Haemorrhage			
subjects affected / exposed	5 / 14 (35.71%)	5 / 15 (33.33%)	
occurrences (all)	5	6	
INR alteration			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	

Vascular disorders			
Arterial hypertension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	3	
Nervous system disorders			
Peripheral neuropathy			
subjects affected / exposed	2 / 14 (14.29%)	5 / 15 (33.33%)	
occurrences (all)	4	8	
Tremor			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	13 / 14 (92.86%)	14 / 15 (93.33%)	
occurrences (all)	27	30	
Leukopenia			
subjects affected / exposed	13 / 14 (92.86%)	12 / 15 (80.00%)	
occurrences (all)	22	24	
Neutropenia			
subjects affected / exposed	14 / 14 (100.00%)	13 / 15 (86.67%)	
occurrences (all)	25	28	
Thrombopenia			
subjects affected / exposed	14 / 14 (100.00%)	15 / 15 (100.00%)	
occurrences (all)	32	38	
General disorders and administration site conditions			
Edema			
subjects affected / exposed	2 / 14 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	2	3	
Fatigue			
subjects affected / exposed	8 / 14 (57.14%)	6 / 15 (40.00%)	
occurrences (all)	12	9	
Fever			
subjects affected / exposed	9 / 14 (64.29%)	9 / 15 (60.00%)	
occurrences (all)	11	12	
Pain			

subjects affected / exposed	7 / 14 (50.00%)	8 / 15 (53.33%)	
occurrences (all)	10	12	
Gastrointestinal disorders			
Mucositis			
subjects affected / exposed	1 / 14 (7.14%)	4 / 15 (26.67%)	
occurrences (all)	2	5	
Nausea			
subjects affected / exposed	4 / 14 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	5	3	
Vomiting			
subjects affected / exposed	3 / 14 (21.43%)	2 / 15 (13.33%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Cough and rhinitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Hypoxia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Ecchymosis and petechias			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Rash/desquamation			
subjects affected / exposed	4 / 14 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	6	4	
Renal and urinary disorders			
Renal function failure			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2	0 / 15 (0.00%) 0	
Infections and infestations Infection with neutropenia subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 6	8 / 15 (53.33%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2009	Protocol Amendment 1 (first approved version)
08 December 2010	clarification total dose vincristine Protocol
08 July 2011	updated safety and risk paragraph due to new IB ed 14 Velcade

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.

Some patients who were not fully eligible in hindsight and slow recruitment.

Notes: