Clinical trial results:
A Phase 3, Multicenter, Randomized, Open-Label, Parallel-Group Study Of The Efficacy And Safety Of Lenalidomide (Revlimid®) Versus Chlorambucil As First-Line Therapy For Previously Untreated Elderly Patients With B-Cell Chronic Lymphocytic Leukemia

Summary

EudraCT number	2008-003079-32
Trial protocol	ES AT BE PT CZ GB HU IT FR NL DK SK BG
Global end of trial date	09 May 2018

Results information

Result version number	v1
This version publication date	25 May 2019
First version publication date	25 May 2019

Trial information

Trial identification

Sponsor protocol code	CC-5013-CLL-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00910910
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 866-260-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Jeffery Jones, MD, Celgene Corporation, 01 908-673-9686, ClinicalTrialDisclosure@Celgene.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	21 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of lenalidomide versus chlorambucil as first-line therapy in elderly patients.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection, Archiving of Essential Documents

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Brazil: 38
Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Croatia: 12
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Hungary: 40
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Russian Federation: 45

Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 63
Worldwide total number of subjects	450
EEA total number of subjects	212

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)	0
From 65 to 84 years	435
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

118 sites randomized participants in Austria, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Columbia, Croatia, Czech Republic, Denmark, Hungary, Israel, Italy, the Netherlands, New Zealand, Poland, Portugal, Romania, Russia, South Africa, Slovakia, Spain, Serbia, the United Kingdom, and the United States of America

Pre-assignment

Screening details:

Participants were randomized 1:1 to lenalidomide or chlorambucil and stratified by disease stage, presence of pre-defined co-morbidities and presence of at least one of the following poor prognostic factors: 11q deletion, 17 p deletion, unmutated IgVH and B2M>4.0 mg/dL.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide

Arm description:

For participants with normal renal function [defined as Creatinine Clearance (CrCL) ≥ 60 mL/min], 5 mg lenalidomide was administered by mouth (PO) once daily (QD) on Days 1 through 28 of the first 28-day cycle, 10 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 15 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until progressive disease (PD) or unacceptable toxicity, whichever occurred first. For participants with moderate renal impairment (defined as CrCL ≥ 30 to < 60 mL/min), 2.5 mg lenalidomide PO QD on Days 1 through 28 of the first 28-day cycle, 5 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 7.5 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until PD or unacceptable toxicity, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	CC-5013
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5 mg lenalidomide PO QD for participants with normal renal function [defined as CrCL ≥ 60 mL/min], on Days 1 through 28 of the first 28-day cycle, 10 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 15 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until PD or unacceptable toxicity, whichever occurred first. For participants with moderate renal impairment (defined as CrCL ≥ 30 to < 60 mL/min), 2.5 mg lenalidomide PO QD on Days 1 through 28 of the first 28-day cycle, 5 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 7.5 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until PD or unacceptable toxicity, whichever occurred first.

Arm title	Chlorambucil

Arm description:

Chlorambucil oral tablets at 0.8 mg/kg on Days 1 and 15 of each 28-day cycle for a total duration of 12 months (approximately 13 cycles).

Arm type	Active comparator

Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	Leukeran
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil tablets at 0.8 mg/kg on Days 1 and 15 of each 28-day cycle

Number of subjects in period 1	Lenalidomide	Chlorambucil
Started	225	225
Safety Population	224	223
Completed	0	1
Not completed	225	224
Adverse event, serious fatal	9	3
Consent withdrawn by subject	7	5
Completed 13 cycles of treatment	-	118
Adverse event, non-fatal	63	35
PD without histologic change	27	23
Unspecified	114	32
Lost to follow-up	2	2
Untreated before cycle 1	1	2
PD with histologic change	-	2
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide
Reporting group description:	
For participants with normal renal function [defined as Creatinine Clearance (CrCL) ≥ 60 mL/min], 5 mg lenalidomide was administered by mouth (PO) once daily (QD) on Days 1 through 28 of the first 28-day cycle, 10 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 15 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until progressive disease (PD) or unacceptable toxicity, whichever occurred first. For participants with moderate renal impairment (defined as CrCL ≥ 30 to < 60 mL/min), 2.5 mg lenalidomide PO QD on Days 1 through 28 of the first 28-day cycle, 5 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 7.5 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until PD or unacceptable toxicity, whichever occurred first.	
Reporting group title	Chlorambucil
Reporting group description:	
Chlorambucil oral tablets at 0.8 mg/kg on Days 1 and 15 of each 28-day cycle for a total duration of 12 months (approximately 13 cycles).	

Reporting group values	Lenalidomide	Chlorambucil	Total
Number of subjects	225	225	450
Age categorical 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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	215	220	435
85 years and over	10	5	15
Age Continuous Units: years			
arithmetic mean	73.0	73.3	
standard deviation	± 5.72	± 5.72	-
Sex: Female, Male			
The Intent-to-Treat (ITT) population was defined as all participants who were randomized, independent of whether they received study treatment or not.			
Units: Subjects			
Female	93	83	176
Male	132	142	274

End points

End points reporting groups

Reporting group title	Lenalidomide

Reporting group description:

For participants with normal renal function [defined as Creatinine Clearance (CrCL) ≥ 60 mL/min], 5 mg lenalidomide was administered by mouth (PO) once daily (QD) on Days 1 through 28 of the first 28-day cycle, 10 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 15 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until progressive disease (PD) or unacceptable toxicity, whichever occurred first. For participants with moderate renal impairment (defined as CrCL ≥ 30 to < 60 mL/min), 2.5 mg lenalidomide PO QD on Days 1 through 28 of the first 28-day cycle, 5 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 7.5 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until PD or unacceptable toxicity, whichever occurred first.

Reporting group title	Chlorambucil

Reporting group description:

Chlorambucil oral tablets at 0.8 mg/kg on Days 1 and 15 of each 28-day cycle for a total duration of 12 months (approximately 13 cycles).

Primary: Kaplan-Meier Estimate of Progression Free Survival (PFS)

End point title	Kaplan-Meier Estimate of Progression Free Survival (PFS)

End point description:

Progression-free survival = the time from randomization to the first documented progression confirmed per investigator's assessment or death due to any cause, whichever occurred first. Progressive disease included lymphadenopathy, an appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates, an increase by 50% or more in greatest determined diameter of any previous site or an increase by 50% or more in the sum of the product of diameters of multiple nodes. The progression date was assigned to the earliest time when any progression was observed without prior missing assessments. If withdrawal of consent or lost to follow-up occurred before progression or death, then these observations were censored at the date when the last complete tumor assessments determined a lack of progression. The ITT population = all subjects who were randomized, independent of whether they received study treatment or not.

End point type	Primary

End point timeframe:

Data cut-off of 18 Feb 2013; up to approximately 39 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212[1]	215		
Units: months				
median (confidence interval 95%)	30.8 (18.7 to 99999)	23.0 (19.3 to 29.2)		

Notes:

[1] - 99999 = The upper boundary of confidence interval (CI) is not estimable because of censored subjects

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratification factors: Disease stage (Binet A or Binet B or Rai I or Rai II versus (VS) Binet C or Rai III or Rai IV); Presence of at least one of the co-morbidities Asparate transaminase (AST)/Alanine

transaminase (ALT) ≥ 3.0 times Upper Limits of Normal (ULN,) Creatinine clearance ≥ 30 to < 60 mL/min, Yes VS No); Presence of at least one 11q deletion, 17p deletion, unmutated Immunoglobulin Heavy-chain Variable-region (IgVH) or Beta-2 Microglobulin (ß2M)> 4.0 mg/L (Yes versus No VS Unknown)

Comparison groups	Lenalidomide v Chlorambucil
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.323
Method	stratified log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.88
upper limit	1.66

Notes:

[2] - Based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Primary: Kaplan-Meier Estimate of Progression Free Survival (PFS) with a Later Cut-off Date

End point title	Kaplan-Meier Estimate of Progression Free Survival (PFS) with a Later Cut-off Date

End point description:

Progression-free survival = the time from randomization to the first documented progression confirmed per investigator's assessment or death due to any cause, whichever occurred first. Progressive disease included lymphadenopathy, an appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates, an increase by 50% or more in greatest determined diameter of any previous site or an increase by 50% or more in the sum of the product of diameters of multiple nodes. The progression date was assigned to the earliest time when any progression was observed without prior missing assessments. If withdrawal of consent or lost to follow-up occurred before progression or death, then these observations were censored at the date when the last complete tumor assessments determined a lack of progression. The Intent-to-Treat (ITT) population = all subjects who were randomized, independent of whether they received study treatment or not.

End point type	Primary

End point timeframe:

From randomization to data cut off date of 26 April 2013; median follow up time for all participants was 12.6 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225[3]	225		
Units: months				
median (confidence interval 95%)	30.8 (18.7 to 99999)	21.4 (19.3 to 25.1)		

Notes:

[3] - 99999= The upper boundary of CI is not estimable because of censored subjects.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratification factors: Disease stage (Binet A or Binet B or Rai I or Rai II versus (VS) Binet C or Rai III or Rai IV); Presence of at least one of the co-morbidities Asparate transaminase (AST)/Alanine transaminase (ALT) ≥ 3.0 times Upper Limits of Normal (ULN,) Creatinine clearance ≥ 30 to < 60 mL/min, Yes VS No); Presence of at least one 11q deletion, 17p deletion, unmutated Immunoglobulin Heavy-chain Variable-region (IgVH) or Beta-2 Microglobulin (ß2M)> 4.0 mg/L (Yes versus No VS Unknown)

Comparison groups	Lenalidomide v Chlorambucil
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.967 [5]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.76
upper limit	1.29

Notes:

[4] - Based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.
[5] - The p-value is based on a stratified log-rank test

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

AEs = any noxious, unintended, or untoward medical occurrence that may appear or worsen during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment, regardless of cause. Serious AE (SAE) = an AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs were graded based on the subjects symptoms according to the Common Terminology Criteria for Adverse Events (Version 4.0) and were evaluated based on following scale -Grade (GR) 1 = Mild - transient or mild discomfort; no medical intervention required; GR 2 - Moderate- mild to moderate limitation in activity; GR 3 = Severe; GR 4 = Life threatening; GR 5 = Death; Safety population = subjects who received at least 1 dose of study drug

End point type	Secondary

End point timeframe:

From randomization up to data cut-off of 18 Feb 2013; Up to approximately 39 months; maximum duration of exposure for Lenalidomide was 1086 days and 406 days for Chlorambucil

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	213		
Units: participants				
≥ 1 TEAE	202	186		
≥ 1 TEAE related to study drug	183	139		
≥ 1 NCI CTC Grade 3-4 TEAE	173	117		
Grade 3-4 adverse event related to any study drug	143	82		

≥ 1 NCI CTC Grade 5 TEAE	21	9		
≥ Grade 5 adverse event related to any study drug	6	1		
≥ 1 Serious TEAE	129	76		
≥ 1 Serious TEAE related to any study drug	95	46		
≥1 TEAE leading to stopping either study drug	61	34		
≥1 Related TEAE leading to stopping either drug	39	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events with a Later Cut-off Date of 31 March 2014

End point title	Number of Participants With Adverse Events with a Later Cut-off Date of 31 March 2014

End point description:

AEs = any noxious, unintended, or untoward medical occurrence that may appear or worsen during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment, regardless of cause. Serious AE (SAE) = an AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs were graded based on the subjects symptoms according to the Common Terminology Criteria for Adverse Events (Version 4.0) and were evaluated based on following scale -Grade (GR) 1 = Mild - transient or mild discomfort; no medical intervention required; GR 2 - Moderate- mild to moderate limitation in activity; GR 3 = Severe; GR 4 = Life threatening; GR 5 = Death; Safety population = subjects who received at least 1 dose of study drug

End point type	Secondary

End point timeframe:

From randomization to the data cut-off of 31 March 2014; Up to 53 months; maximum duration of exposure for Lenalidomide was 1140 days and 406 days for Chlorambucil

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	223		
Units: participants				
≥ 1 TEAE	216	202		
≥ 1 TEAE related to study drug	194	155		
≥ 1 NCI CTC Grade 3-4 TEAE	188	131		
Grade 3-4 adverse event related to any study drug	157	90		
≥ 1 NCI CTC Grade 5 TEAE	21	11		
≥ Grade 5 adverse event related to any study drug	6	1		
≥ 1 Serious TEAE	148	90		
≥ 1 Serious TEAE related to any study drug	107	53		
≥1 TEAE leading to stopping either study drug	70	42		

≥1 Related TEAE leading to stopping either drug	46	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with the Best Overall Response Based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines

End point title	Percentage of Participants with the Best Overall Response Based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines

End point description:

A best overall response rate is a CR, CRi, nPR or PR and is defined as: Complete Remission (CR): • No lymphadenopathy • No hepatomegaly or splenomegaly • Absence of constitutional symptoms • Polymorphonuclear leukocytes ≥ 1500/ul • No circulating clonal B-lymphocytes • Platelets > 100,000/ul • Hemoglobin >11.0 g/dl • Normocellular <30% lymphocytes, no B-lymphoid nodules; Incomplete Clinical Response (CRi): • CR without bone marrow biopsy confirmation. Nodular Partial Response (nPR): • CR with the presence of residual clonal nodules. Partial Response (PR) requires: • ≥ 50% decrease in peripheral blood lymphocyte count • ≥ 50% reduction in lymphadenopathy • ≥ 50% reduction in size of liver and/or spleen • 1 or more of the following:• Polymorphonuclear leukocytes ≥ 1500/ul • Platelets >100,000/ul. A smaller population was used (earlier cut-off date) prior to the last subject enrolled. The ITT population = all subjects who were randomized, independent of whether they received study drug

End point type	Secondary

End point timeframe:

Up to data cut-off of 18 Feb 2013; approximately 39 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	215		
Units: percentage of participants				
number (not applicable)	51.9	62.3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Chlorambucil
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.96

Secondary: Percentage of Participants with a Best Overall Response based on IWCLL Guidelines with a Later Cut-off Date of 31 March 2014

End point title	Percentage of Participants with a Best Overall Response based on IWCLL Guidelines with a Later Cut-off Date of 31 March 2014

End point description:

A best overall response rate is a CR, CRi, nPR or PR and is defined as: Complete Remission (CR): • No lymphadenopathy • No hepatomegaly or splenomegaly • Absence of constitutional symptoms • Polymorphonuclear leukocytes ≥ 1500/ul • No circulating clonal B-lymphocytes • Platelets > 100,000/ul • Hemoglobin > 11.0 g/dl • Normocellular <30% lymphocytes, no B-lymphoid nodules; Incomplete Clinical Response (CRi): • CR without bone marrow biopsy confirmation. Nodular Partial Response: • CR with the presence of residual clonal nodules. Partial Response requires: • ≥ 50% decrease in peripheral blood lymphocyte count • ≥ 50% reduction in lymphadenopathy • ≥ 50% reduction in size of liver and/or spleen • 1 or more of the following: • Polymorphonuclear leukocytes ≥ 1500/ul • Platelets >100,000/ul. The Intent-to-Treat population was defined as all participants who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

Up to data cut-off of 31 March 2014; approximately 53 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	225		
Units: percentage of participants				
number (not applicable)	60.9	70.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Chlorambucil
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.98

Secondary: Kaplan-Meier Estimate for Duration of Response

End point title	Kaplan-Meier Estimate for Duration of Response

End point description:

Duration of response was defined as the time from first nPR, PR, CRi, or CR to PD. Duration of response was censored at the last date that the patient was known to be progression-free for: 1) patients who had not progressed at the time of analysis; 2) patients who had withdrawn consent or were lost to follow-up prior to documentation of progression. Intent to Treat population with an objective response as of 18 Feb 2013; includes responders.

End point type	Secondary

End point timeframe:

Up to data cut-off of 18 Feb 2013; up to approximately 39 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110[6]	134		
Units: weeks				
median (confidence interval 95%)	99999 (131.1 to 99999)	105.3 (77.4 to 123.7)		

Notes:

[6] - 99999 = Due to large number of censored observations.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Chlorambucil
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.826
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.58
upper limit	1.52

Notes:

[7] - Based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Secondary: Kaplan-Meier Estimate for Duration of Response with a Later Cut-off Date of 31 March 2014

End point title	Kaplan-Meier Estimate for Duration of Response with a Later Cut-off Date of 31 March 2014

End point description:

Duration of response was defined as the time from first nPR, PR, CRi, or CR to PD. Duration of response was censored at the last date that the patient was known to be progression-free for: 1) participants who had not progressed at the time of analysis; 2) participants who had withdrawn consent or were lost to follow-up prior to documentation of progression. Intent to Treat population with an objective response as of 31 March 2014; includes responders.

End point type	Secondary

End point timeframe:

Up to data cut-off of 31 March 2014; up to approximately 53 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137[8]	158		
Units: weeks				
median (confidence interval 95%)	99999 (149.4 to 99999)	87.1 (77.1 to 108.7)		

Notes:

[8] - 99999 = The median and upper boundary of CI is not estimable because of censored subjects.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Chlorambucil
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.149
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.48
upper limit	1.05

Notes:

[9] - Based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was calculated as the time from randomization to the first nPR, PR, CRi or CR based on IWCLL guidelines. The Intent to Treat participants with an objective response as of 18 February 2013.

End point type	Secondary

End point timeframe:

Up to data cut-off of 18 Feb 2013; up to approximately 39 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	134		
Units: weeks				
median (full range (min-max))	8.6 (3.7 to 104.3)	8.1 (3.7 to 52.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response for a Later Cut-off Date of 31 March 2014

End point title	Time to Response for a Later Cut-off Date of 31 March 2014

End point description:

Time to response was calculated as the time from randomization to the first nPR, PR, CRi or CR based on IWCLL guidelines. ITT participants who had not progressed at the time of analysis; or those who had withdrawn consent or were lost to follow-up prior to documentation of progression.

End point type	Secondary

End point timeframe:

Up to data cut-off of 31 March 2014; up to approximately 53 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	158		
Units: weeks				
median (full range (min-max))	10.4 (3.7 to 136.1)	8.1 (3.7 to 68.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Overall Survival

End point title	Kaplan Meier Estimate of Overall Survival

End point description:

Overall Survival is defined as the time between randomization and death from any cause. 99999 = the median OS was not reached due to the long survival of the subjects relative to the study duration. The Intent-to-Treat population was defined as all participants who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

Up to data cut off of 31 March 2014; median follow-up for all participants was 18.8 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225[10]	225[11]		
Units: Months				
median (confidence interval 95%)	99999 (-99999 to 99999)	44.0 (37.3 to 99999)		

Notes:

[10] - 99999 = The median has not been reached and CI not estimable because of small number of events.
[11] - 99999 = median OS was not reached due to the long survival relative to the study duration

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Chlorambucil
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.883
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.46

Notes:

[12] - Based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Secondary: Kaplan Meier Estimate for Overall Survival with a Later Cut-off Date of 21 June 2018

End point title	Kaplan Meier Estimate for Overall Survival with a Later Cut-off Date of 21 June 2018

End point description:

Overall Survival (OS) is defined as the time between randomization and death from any cause. 99999 = the median OS was not reached due to the long survival of the subjects relative to the study duration. The ITT population was defined as all participants who were randomized, independent of whether they received study treatment.

End point type	Secondary

End point timeframe:

Up to the final data cut off date of 21 June 2018; median follow-up for all participants was 46.7 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	225[13]		
Units: Months				
median (confidence interval 95%)	74.3 (58.5 to 84.4)	70.5 (57.1 to 99999)		

Notes:

[13] - 99999 = Upper CI not estimable because of censored observations.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Chlorambucil
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.709
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.83
upper limit	1.34

Notes:

[14] - Based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups

Secondary: Functional Assessment of Cancer Therapy-General to Create the FACT-Leukemia (FACT-Leu) Quality of Life Instrument

End point title	Functional Assessment of Cancer Therapy-General to Create the FACT-Leukemia (FACT-Leu) Quality of Life Instrument

End point description:

The FACT-Leu scale is a valid, reliable, and efficient measure of leukemia-specific health-related quality of life for acute and chronic disease. The FACT-Leu is described as including 27 items that assess 17 physical symptoms (fevers, bleeding, general pain, stomach pain, chills, night sweats, bruising, lymph node swelling, weakness, tiredness, weight loss, appetite, shortness of breath, functional ability, diarrhea, concentration, and mouth sores) and 10 emotional/social concerns (frustration with activity limitation, discouraged by illness, future planning, uncertainty, worry about illness, emotional lability, isolation, infertility concern, family worry, and worry about infections). No data were collected for the FACT-Leu QOL assessment. Analysis was not conducted due to the discontinuation of the lenalidomide arm.

End point type	Secondary

End point timeframe:

Day 1 and once every 8 weeks

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: participants				
number (not applicable)				

Notes:

[15] - Analysis not conducted due to the discontinuation of the lenalidomide arm.

[16] - Analysis not conducted due to the discontinuation of the lenalidomide arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Euro Quality of Life Five Dimension (EQ-5D) Questionnaire

End point title	Euro Quality of Life Five Dimension (EQ-5D) Questionnaire

End point description:

The standardized extended version of EQ-5D was designed for the collection of health state values using a visual analogue scale (VAS) rating scale - a vertical 20 cm visual analogue scale with the end points labeled best imaginable health state at the top and worst imaginable health state at the bottom having numeric values of 100 and 0 respectively. The participant is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. No data were collected for the EQ-5D QOL assessment. The EQ-5D analysis was not conducted due to the discontinuation of the lenalidomide arm.

End point type	Secondary

End point timeframe:

Day 1 and once every 8 weeks

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: participants				
number (not applicable)				

Notes:

[17] - Analysis not conducted due to the discontinuation of the lenalidomide arm

[18] - Analysis not conducted due to the discontinuation of the lenalidomide arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants and Types of Subsequent Anti-cancer Therapies Received Post Treatment

End point title	Number of Participants and Types of Subsequent Anti-cancer Therapies Received Post Treatment

End point description:

Subsequent anti-cancer therapies administered to participants following the discontinuation of study drug (either Lenalidomide or Chlorambucil). ITT population includes all participants who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

Up to the final data cut off date of 21 June 2018; ; median follow-up for all participants 46.7 months

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	223		
Units: participants				
Participants Receiving Additional CLL Therapy	125	120		
Participants Receiving Alkylating Agents	107	106		
Participants Receiving Antineoplastic Agents	93	86		
Participants Receiving Antimetabolites	34	24		
Participants Receiving Corticosteroids	27	16		
Participants Receiving Plant Alkaloids	22	11		
Participants Receiving Cytotoxic Antibiotic	10	3		
Participants Receiving Immunosuppressants	3	2		
Participants Receiving Therapeutic Products	4	3		
Participants Receiving Other Unspecified Products	0	2		
Antihistamine For Systemic Use	1	1		
Drugs for Peptic Ulcer and Gastric Reflex	1	0		
Immunoglobulins	1	2		
Other Analgesics and Antipyretics	1	1		
Specific Antirheumatic Agents	1	0		
Antiemetics and Antinauseants	0	1		
Corticosteriods for Systemic Use	0	1		
Immunostimulants	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants Deaths During the Treatment and Survival Follow-Up Phase

End point title	Number of Participants Deaths During the Treatment and Survival Follow-Up Phase

End point description:

The number of study participants deaths during the treatment and follow-up phase

End point type	Other pre-specified

End point timeframe:

Up to final date cut-off date of 21 June 2018; from the date of the first dose of investigational product to death

End point values	Lenalidomide	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	225		
Units: Participants	101	95		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were recorded by the Investigator(s) from first dose of study drug to 30 days after the treatment discontinuation visit. The median treatment duration was 263 days for lenalidomide and 362 days for chlorambucil.

Adverse event reporting additional description:

Secondary Primary Malignancies (SPMs) were monitored and are reported as SAEs regardless of the arm the participant was is in. These are reported from the time of signing the informed consent up to and including the survival follow-up period. Participants were followed for at least 5 years from the date the last patient was randomized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Chlorambucil

Reporting group description:

Chlorambucil oral tablets at 0.8 mg/kg on Days 1 and 15 of each 28-day cycle for a total duration of 12 months

Reporting group title	Lenalidomide

Reporting group description:

For participants with normal renal function [defined as Creatinine Clearance (CrCL) ≥ 60 mL/min], 5 mg lenalidomide was administered by mouth (PO) once daily (QD) on Days 1 through 28 of the first 28-day cycle, 10 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 15 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until progressive disease (PD) or unacceptable toxicity, whichever occurred first. For participants with moderate renal impairment (defined as CrCL ≥ 30 to < 60 mL/min), 2.5 mg lenalidomide PO QD on Days 1 through 28 of the first 28-day cycle, 5 mg lenalidomide PO QD on Days 1 through 28 starting at cycle 2, 7.5 mg lenalidomide PO QD starting at cycle 3 and for the remainder of the study until PD or unacceptable toxicity, whichever occurred first.

Serious adverse events	Chlorambucil	Lenalidomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 223 (40.36%)	148 / 224 (66.07%)	
number of deaths (all causes)	11	21	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA PANCREAS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			

subjects affected / exposed	8 / 223 (3.59%)	5 / 224 (2.23%)	
occurrences causally related to treatment / all	0 / 9	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASOSQUAMOUS CARCINOMA OF SKIN			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BOWEN'S DISEASE			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CANCER			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC LYMPHOCYTIC LEUKAEMIA			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
COLON ADENOMA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CANCER			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HODGKIN'S DISEASE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG NEOPLASM MALIGNANT			

subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG SQUAMOUS CELL CARCINOMA STAGE II			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO LIVER			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTATIC MALIGNANT MELANOMA			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RICHTER'S SYNDROME			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN CANCER			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			

subjects affected / exposed	7 / 223 (3.14%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	5 / 21	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR FLARE			
subjects affected / exposed	0 / 223 (0.00%)	8 / 224 (3.57%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 223 (0.45%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE CRISIS			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LERICHE SYNDROME			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERY ANEURYSM			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SHOCK			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
THROMBOPHLEBITIS SUPERFICIAL			

subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS LIMB			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 223 (1.35%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	2 / 223 (0.90%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTI-ORGAN FAILURE			
subjects affected / exposed	0 / 223 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	2 / 3	
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	6 / 223 (2.69%)	10 / 224 (4.46%)	
occurrences causally related to treatment / all	1 / 7	2 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN CARDIAC DEATH			

subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
BRONCHIECTASIS			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 223 (0.45%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 223 (0.45%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFILTRATION			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

PLEURAL EFFUSION			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY ALVEOLAR HAEMORRHAGE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 223 (0.45%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY HYPERTENSION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
SINUS CONGESTION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD UREA INCREASED			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD INJURY			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

HIP FRACTURE			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKULL FRACTURE			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR PSEUDOANEURYSM			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			

subjects affected / exposed	1 / 223 (0.45%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK FIRST DEGREE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 223 (0.00%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
CARDIAC FAILURE			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIAC FAILURE ACUTE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC FAILURE CONGESTIVE			

subjects affected / exposed	0 / 223 (0.00%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOGENIC SHOCK			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOPULMONARY FAILURE			
subjects affected / exposed	0 / 223 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
CONGESTIVE CARDIOMYOPATHY			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 223 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
SICK SINUS SYNDROME			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR TACHYCARDIA			

subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL INFARCTION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL ISCHAEMIA			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONVULSION			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEMIPARESIS			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			

subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SIMPLE PARTIAL SEIZURES			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 223 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 223 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
AGRANULOCYTOSIS			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAEMIA			
subjects affected / exposed	10 / 223 (4.48%)	18 / 224 (8.04%)	
occurrences causally related to treatment / all	8 / 18	16 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
AUTOIMMUNE HAEMOLYTIC ANAEMIA			
subjects affected / exposed	4 / 223 (1.79%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
FEBRILE NEUTROPENIA			

subjects affected / exposed	3 / 223 (1.35%)	7 / 224 (3.13%)	
occurrences causally related to treatment / all	2 / 3	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IDIOPATHIC THROMBOCYTOPENIC PURPURA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOPENIA			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	33 / 223 (14.80%)	54 / 224 (24.11%)	
occurrences causally related to treatment / all	48 / 54	108 / 117	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPLENIC HAEMORRHAGE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	13 / 223 (5.83%)	19 / 224 (8.48%)	
occurrences causally related to treatment / all	13 / 18	32 / 35	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
DIPLOPIA			

subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MACULOPATHY			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	2 / 223 (0.90%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN LOWER			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL HERNIA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			

subjects affected / exposed	2 / 223 (0.90%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	2 / 223 (0.90%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (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	3 / 223 (1.35%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS CHRONIC			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			

subjects affected / exposed	2 / 223 (0.90%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS TOXIC			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
BLISTER			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG ERUPTION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EXFOLIATIVE RASH			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	1 / 223 (0.45%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH GENERALISED			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULO-PAPULAR			

subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STEVENS-JOHNSON SYNDROME			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URTICARIA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL COLIC			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 223 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHROPATHY			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

BACK PAIN			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLANK PAIN			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ANAL ABSCESS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS BACTERIAL			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	1 / 223 (0.45%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

BRONCHITIS BACTERIAL			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 223 (0.45%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	3 / 223 (1.35%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS STAPHYLOCOCCAL			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA INFECTIOUS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROBACTER SEPSIS			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA SEPSIS			

subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALISED INFECTION			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 223 (0.45%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			

subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC INFECTION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCOCCAL SEPSIS			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	6 / 223 (2.69%)	24 / 224 (10.71%)	
occurrences causally related to treatment / all	3 / 9	15 / 34	
deaths causally related to treatment / all	1 / 3	3 / 5	
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	4 / 223 (1.79%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 6	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPSIS SYNDROME			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			

subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONSILLITIS			
subjects affected / exposed	1 / 223 (0.45%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 223 (0.45%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS INFECTIVE			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	3 / 223 (1.35%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	2 / 223 (0.90%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GOUT			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			

subjects affected / exposed	1 / 223 (0.45%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCAEMIA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 223 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	3 / 223 (1.35%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	0 / 223 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Chlorambucil	Lenalidomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	184 / 223 (82.51%)	204 / 224 (91.07%)	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	7 / 223 (3.14%)	14 / 224 (6.25%)	
occurrences (all)	14	23	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	7 / 223 (3.14%)	14 / 224 (6.25%)	
occurrences (all)	10	18	
BLOOD CREATININE INCREASED			

subjects affected / exposed	7 / 223 (3.14%)	22 / 224 (9.82%)	
occurrences (all)	11	60	
WEIGHT DECREASED			
subjects affected / exposed	23 / 223 (10.31%)	34 / 224 (15.18%)	
occurrences (all)	26	47	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR FLARE			
subjects affected / exposed	11 / 223 (4.93%)	85 / 224 (37.95%)	
occurrences (all)	11	166	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	12 / 223 (5.38%)	16 / 224 (7.14%)	
occurrences (all)	12	19	
HEADACHE			
subjects affected / exposed	11 / 223 (4.93%)	16 / 224 (7.14%)	
occurrences (all)	23	24	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	46 / 223 (20.63%)	69 / 224 (30.80%)	
occurrences (all)	102	133	
NEUTROPENIA			
subjects affected / exposed	74 / 223 (33.18%)	126 / 224 (56.25%)	
occurrences (all)	195	576	
THROMBOCYTOPENIA			
subjects affected / exposed	50 / 223 (22.42%)	72 / 224 (32.14%)	
occurrences (all)	114	228	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	10 / 223 (4.48%)	19 / 224 (8.48%)	
occurrences (all)	11	31	
FATIGUE			
subjects affected / exposed	53 / 223 (23.77%)	66 / 224 (29.46%)	
occurrences (all)	86	109	
OEDEMA PERIPHERAL			
subjects affected / exposed	16 / 223 (7.17%)	43 / 224 (19.20%)	
occurrences (all)	23	65	

PYREXIA			
subjects affected / exposed	18 / 223 (8.07%)	37 / 224 (16.52%)	
occurrences (all)	25	61	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	10 / 223 (4.48%)	30 / 224 (13.39%)	
occurrences (all)	15	36	
CONSTIPATION			
subjects affected / exposed	17 / 223 (7.62%)	28 / 224 (12.50%)	
occurrences (all)	23	39	
DIARRHOEA			
subjects affected / exposed	32 / 223 (14.35%)	66 / 224 (29.46%)	
occurrences (all)	45	117	
NAUSEA			
subjects affected / exposed	63 / 223 (28.25%)	33 / 224 (14.73%)	
occurrences (all)	100	47	
VOMITING			
subjects affected / exposed	28 / 223 (12.56%)	11 / 224 (4.91%)	
occurrences (all)	48	15	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	21 / 223 (9.42%)	38 / 224 (16.96%)	
occurrences (all)	25	48	
DYSPNOEA			
subjects affected / exposed	12 / 223 (5.38%)	21 / 224 (9.38%)	
occurrences (all)	16	28	
Skin and subcutaneous tissue disorders			
NIGHT SWEATS			
subjects affected / exposed	14 / 223 (6.28%)	24 / 224 (10.71%)	
occurrences (all)	15	34	
PRURITUS			
subjects affected / exposed	7 / 223 (3.14%)	18 / 224 (8.04%)	
occurrences (all)	11	24	
RASH			
subjects affected / exposed	19 / 223 (8.52%)	41 / 224 (18.30%)	
occurrences (all)	23	76	

Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	11 / 223 (4.93%)	14 / 224 (6.25%)	
occurrences (all)	15	17	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	12 / 223 (5.38%)	15 / 224 (6.70%)	
occurrences (all)	16	27	
BACK PAIN			
subjects affected / exposed	18 / 223 (8.07%)	28 / 224 (12.50%)	
occurrences (all)	21	37	
MUSCLE SPASMS			
subjects affected / exposed	5 / 223 (2.24%)	15 / 224 (6.70%)	
occurrences (all)	5	20	
PAIN IN EXTREMITY			
subjects affected / exposed	4 / 223 (1.79%)	16 / 224 (7.14%)	
occurrences (all)	5	23	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	4 / 223 (1.79%)	16 / 224 (7.14%)	
occurrences (all)	4	20	
INFLUENZA			
subjects affected / exposed	2 / 223 (0.90%)	13 / 224 (5.80%)	
occurrences (all)	2	14	
NASOPHARYNGITIS			
subjects affected / exposed	3 / 223 (1.35%)	12 / 224 (5.36%)	
occurrences (all)	4	14	
PNEUMONIA			
subjects affected / exposed	1 / 223 (0.45%)	13 / 224 (5.80%)	
occurrences (all)	2	15	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	11 / 223 (4.93%)	16 / 224 (7.14%)	
occurrences (all)	12	22	
Metabolism and nutrition disorders			
DECREASED APPETITE			

subjects affected / exposed	13 / 223 (5.83%)	30 / 224 (13.39%)	
occurrences (all)	18	42	
HYPERKALAEMIA			
subjects affected / exposed	4 / 223 (1.79%)	12 / 224 (5.36%)	
occurrences (all)	4	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2009	1. Modified language about anti-thrombotic therapy to be consistent with other CLL protocols. 2. Deleted inclusion criterion (must not have received a prior treatment for B-cell CLL) as this was listed as an exclusion criterion (Prior treatment for B-cell CLL). 3. Deleted exclusion criterion (uncontrolled hyperthyroidism or hypothyroidism) 4. Added the exclusion criterion (serum total bilirubin > 1.5 x ULN, except in case of hemolytic anemia or Gilbert's syndrome) and deleted co-morbidity of bilirubin ≥ 2.0 times ULN, with the exception of Gilbert's syndrome. 5. Added nPR as a response and changed the CR/CRi confirmation visit to ≥ 8 weeks after all clinical and laboratory response criteria had been met to be consistent with December 2008 Hallek criteria. 6. Changed the time for retesting peripheral blood and bone marrow for MRD status from 16 weeks to 8 weeks for subjects who reached CR/CRi with blood negativity achieved within the 6 months after the CR/CRi confirmation visit and the bone marrow was still MRD positive. 7. Added that if bone marrow was hypocellular at the CR/CRi confirmation visit, a repeat specimen (including adequate biopsy sample) was to be obtained 4 weeks later provided that blood counts had recovered. 8. Clarified that allopurinol therapy was to be started only after confirmation of the subject's eligibility in the study. 9. Removed ibuprofen as a suggested treatment for ≥ Grade 2 tumor flare because of the potential impact of ibuprofen on renal function. 10. Added a pregnancy test assessment at Study Day 1 for subjects in the chlorambucil arm. 11. Changed the Broca's index to formula referenced in the Robinson, 1983 article. 12. Added dose reduction and modification guidelines for changes in liver function. 13. Clarified that thyroid function tests were required for all subjects at screening and for subjects in the lenalidomide arm at additional specified intervals during the study.
23 October 2009	1. Corrected the disease stage stratification to include Binet Stage B with the Rai Stage I and II category instead of the Rai Stage III and IV category. 2. Allowed the splitting of the chlorambucil dose over 2 days for subjects who could not swallow a full dose in 1 day and allowed the used of systemic anti-emetics prior to chlorambucil treatment. 3. Clarified that the MRD analysis was to be repeated each time a CR/CRi confirmation was performed. For this analysis, an additional peripheral blood sample was to be collected. 4. Limited allopurinol use for TLS prophylaxis to allopurinol 300 mg/day for 3 days prior to starting study treatment and for the first cycle of treatment for subjects in the chlorambucil arm, and added guidance that all subjects entering the study on allopurinol for an indication other than TLS were to continue on their prescribed dose according to the stipulated guidance. 5. Modified the required prophylaxis regimen for thromboembolic events; additional guidance was added to allow investigators to choose the most appropriate anti-thrombotic therapy based on subject's thrombotic and bleeding risks. 6. Allowed the investigators more flexibility for the treatment of ≥ Grade 1 TLS. 7. Add an exclusion criterion for subjects with a known allergy to allopurinol.

15 January 2010	1. Added guidance to investigators to interrupt, adjust, or discontinue anti-thrombotic treatment for subjects with platelet counts < 50,000/µL and for subjects with platelet count < 20,000/µL. 2. Added guidance to investigators that Study Day 1 laboratory values were to be carefully reviewed within the first few days of study therapy initiation and appropriate dose reductions/interruptions made based on these results and that clinical assessments (physical examination and vital signs) were to be carefully assessed on Study Day 1 prior to subjects entering the study. 3. Corrected the formula used to determine Broca's ideal weight for women.
11 April 2011	1. Deleted the exclusion criterion for subjects with uncontrolled hyperthyroidism or hypothyroidism. 2. Changed the visit schedule to reduce the number of visits in Cycle 1 and Cycle 2 and the first and second cycle of each dose escalation. 3. Defined the end of study as the time when all subjects had been followed for at least 5 years following randomization and when at least 284 deaths had occurred. 4. Allowed the use of historic/archived bone marrow core or 10-cut, unstained biopsy slides that had been collected within 60 days of screening for the purposes of the screening histology review. 5. Allowed the use of peripheral blood for FISH, ZAP-70, IgVH mutational status analyses and storage obtained within 84 days of Study Day 1 as the screening sample for subjects who were re-screened. 6. Required that all subjects who discontinued treatment or the progression-free follow up phase for reasons other than PD be followed until PD and/or death. 7. Added quality of life assessments during the Survival Follow-Up Phase. 8. Required that subjects with decreased renal function (CrCL ≥ 30 to < 60 mL/min) take a reduced dose of 100 mg of allopurinol. 9. Modified the allopurinol treatment schedule for subjects on lenalidomide to the first cycle of treatment and the first cycle of each dose escalation. 10. Allowed subjects with carcinoma in situ of the bladder to enroll in the study. 11. Corrected the timing of the first ECG from Cycle 4, Day 1 to Cycle 5, Day 1. 12. Deleted the requirement for a bone marrow aspirate and biopsy to be collected for molecular CR determination. 13. Required SMPs to be treated as SAEs and reported throughout study.
10 November 2011	1. Changed the exclusion criteria for subjects with a history of prior malignancies from 3 years to ≥ 5 years. 2. Added exploratory analyses of biomarkers of study drug activity (DNA, RNA, protein). 3. Clarified that the thyroid function tests for subjects on lenalidomide, and the ECG and Quality-of-Life questionnaires for subjects in both arms were not required during drug holds. 4. Required all Grade 3 hematologic laboratory abnormalities to be reported as AEs on the AE page of the eCRF.
06 May 2013	1. Required the immediate discontinuation of study drug, regardless of treatment assignment, for all subjects 81 years of age or older at the time of signing the informed consent, and provided guidance for subsequent follow-up for these subjects and for subjects 70 to 80 years of age at the time of signing the informed consent who continued in the study.
02 August 2013	1. Required the immediate discontinuation of lenalidomide treatment for all subjects randomized to the lenalidomide arm and provided guidance for subsequent follow-up for these subjects. 2. Allowed subjects in the chlorambucil arm to continue to receive study drug at the discretion of the investigator for a total duration of 13 cycles (approximately 12 months) or until PD or unacceptable toxicity developed, whichever occurred first. 3. Deleted all efficacy assessments. 4. Deleted the 28-day progression-free follow-up period and required that all subjects enter the survival follow-up period and were contacted every 4 months to collect information on SPMs, OS, and other anti cancer CLL therapies for at least 5 years after the last subject was randomized.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 July 2012	The FDA placed the study on partial clinical hold due to the greater number of deaths reported in the lenalidomide arm compared with the chlorambucil arm, and a trend in overall survival in favor of chlorambucil.	02 August 2013

Notes:

Limitations and caveats

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

After notification by the US Food and Drug Administration on 12Jul2013, Celgene agreed to stop lenalidomide due to an imbalance in the number of deaths on the lenalidomide arm versus the chlorambucil arm; no causality for the imbalance was identified

Notes: