Clinical trial results:
Sub-cutaneous Rituximab-miniCHOP versus Sub-cutaneous Rituximab-miniCHOP + lenalidomide (R2-miniCHOP) in Diffuse Large B Cell Lymphoma for patients of 80 years old or more. A multicentric phase III study of the LYSA.

Summary

EudraCT number	2013-000450-22
Trial protocol	BE PT
Global end of trial date	07 February 2021

Results information

Result version number	v1 (current)
This version publication date	08 January 2023
First version publication date	08 January 2023
Summary attachment (see zip file)	SENIOR synopsis CSR (SENIOR CSR Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	SENIOR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02128061
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	Centre Hospitalier Lyon-Sud Bâtiment 2D, Pierre Benite, France,
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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	28 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the study is to compare the efficacy of R2-miniCHOP and R-miniCHOP in patients ≥ 80 years with not previously treated CD20+ diffuse large B-cell lymphoma as measured by the overall survival (OS)

Protection of trial subjects:

In case of deep vein thrombosis (DVT) occurrence, antithrombotic treatment (heparin or Coumadin [INR 2-3]) must be started (and kept during the whole treatment duration with lenalidomide) and lenalidomide can be resumed without dose reduction.
If DVT is not resolved or in case of DVT recurrence, lenalidomide must be stopped and the decision of maintaining the R-miniCHOP regimen stays at the investigator's discretion.

Background therapy:

R-miniCHOP

Evidence for comparator:

In Phase II study of the GELA group involving patients older than 80 years, the efficacy and safety of a decreased dose of CHOP (doxorubicin, cyclophosphamide, vincristine, and prednisone) chemotherapy with a conventional dose of rituximab (R-miniCHOP) was recently investigated. After a median follow-up of 20 months, analysis by intention to treat of the 149 included patients demonstrated a 2-year overall survival of 59%, a 2-year PFS of 47% and a median progression-free survival of 21 months. The most frequent side-effect was haematological toxicity (grade ≥ 3 neutropenia in 40% of cases) but with infrequent febrile neutropenia (7%) indicating that R-miniCHOP displays a good compromise between efficacy and safety in this population10. This regimen can be considered as the current gold standard for fit patients older than 80 years. According to further multivariate analysis performed for this study (not published), survival of patients less than 85 years was significantly different from patients aged of more than 85 years old. Similar results were obtained in a 70% CHOP reduction regimen for patients older than 70, displaying a 3-year PFS of 72% and a 3-year OS of 58%21. Activity and safety of dose-adjusted infusional cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (DA-EPOCH) with rituximab in elderly patients with poor-prognostic untreated DLBCL has been also proposed in frail patients older than 70 years.
To date, the R-miniCHOP (with rituximab IV) regimen is the standard of care for fit DLBCL patients > 80y and will be the standard arm of the trial.

Actual start date of recruitment	31 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	France: 237

Worldwide total number of subjects	249
EEA total number of subjects	249

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	188
85 years and over	61

Subject disposition

Recruitment

Recruitment details:

250 patients were randomized at 71 study centers in France, Belgium and Portugal from August 20th, 2014 to September 13th, 2017.

Pre-assignment

Screening details:

In both arms, before the start of the treatment and after randomization, a pre-phase treatment was administered to the patients one week before D1 of chemotherapy.
Chemotherapy regimen :
-Prednisone 60 mg/m2 at D-7 D-6 D-5 D-4
-Vincristine 1 mg TD at D-7

Period 1

Period 1 title	Pre-Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	R-mini chop

Arm description:

Standard Arm : All patients will be treated with R-miniCHOP at a three-weeks interval for 6 cycles

CYCLOPHOSPHAMIDE IV (400 mg/m² at D1)
DOXORUBICINE IV (25 mg/m² at D1)
VINCRISTINE IV (1 mg TD at D1)
PREDNISONE PO (40 mg/m² from D1 to D5)
RITUXIMAB SC* (1400 mg TD at D1)
*The first cycle of rituximab is delivered by IV at the dose of 375 mg/m2

Arm type	Standard
Investigational medicinal product name	VINCRISTINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg TD

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

Dosage and administration details:

60 mg/m2

Arm title	R2-minichop

Arm description:

Experimental Arm : All patients will be treated with R2-miniCHOP at a three-weeks interval for 6 cycles

CYCLOPHOSPHAMIDE IV (400 mg/m² at D
DOXORUBICINE IV (25 mg/m² at D1)

VINCRISTINE IV (1 mg TD at D1)
PREDNISONE PO (40 mg/m² from D1 to D5)
RITUXIMAB SC* (1400 mg TD at D1)
LENALIDOMIDE PO** (10 mg TD from D1 to D14)

Arm type	Experimental
Investigational medicinal product name	VINCRISTINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg TD

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

Dosage and administration details:

60 mg/m2

Number of subjects in period 1	R-mini chop	R2-minichop
Started	127	122
Completed	127	122

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	R-mini chop

Arm description:

Standard Arm : All patients will be treated with R-miniCHOP at a three-weeks interval for 6 cycles

CYCLOPHOSPHAMIDE IV (400 mg/m² at D1)
DOXORUBICINE IV (25 mg/m² at D1)
VINCRISTINE IV (1 mg TD at D1)
PREDNISONE PO (40 mg/m² from D1 to D5)
RITUXIMAB SC* (1400 mg TD at D1)
*The first cycle of rituximab is delivered by IV at the dose of 375 mg/m2

Arm type	Standard

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

375 mg/m2
1400 mg TD

Investigational medicinal product name	CYCLOPHOSPHAMIDE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m²

Investigational medicinal product name	DOXORUBICINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection

Dosage and administration details:

25 mg/m²

Investigational medicinal product name	VINCRISTINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg TD

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

Dosage and administration details:

40 mg/m²

Arm title	R2-minichop

Arm description:

Experimental Arm : All patients will be treated with R2-miniCHOP at a three-weeks interval for 6 cycles

CYCLOPHOSPHAMIDE IV (400 mg/m² at D
DOXORUBICINE IV (25 mg/m² at D1)
VINCRISTINE IV (1 mg TD at D1)
PREDNISONE PO (40 mg/m² from D1 to D5)
RITUXIMAB SC* (1400 mg TD at D1)
LENALIDOMIDE PO** (10 mg TD from D1 to D14)

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 10 mg TD	
Investigational medicinal product name	CYCLOPHOSPHAMIDE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m²	
Investigational medicinal product name	VINCRISTINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use
Dosage and administration details: 1 mg TD	
Investigational medicinal product name	DOXORUBICINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection
Dosage and administration details: 25 mg/m²	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use
Dosage and administration details: 375 mg/m2 1400 mg TD	

Number of subjects in period 2	R-mini chop	R2-minichop
Started	127	122
Completed	100	101
Not completed	27	21
Consent withdrawn by subject	-	2
Adverse event, non-fatal	7	6
Death	5	2
Progression	9	3
other	-	1
Toxicity of study treatment	2	5
voluntary treatment discontinuation	-	1
Protocol deviation	1	1
Lack of efficacy	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Pre-Phase

Reporting group description: -

Reporting group values	Pre-Phase	Total	
Number of subjects	249	249	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	188	188	
85 years and over	61	61	
Gender categorical Units: Subjects			
Female	136	136	
Male	113	113	

End points

End points reporting groups

Reporting group title	R-mini chop

Reporting group description:

Standard Arm : All patients will be treated with R-miniCHOP at a three-weeks interval for 6 cycles

CYCLOPHOSPHAMIDE IV (400 mg/m² at D1)
DOXORUBICINE IV (25 mg/m² at D1)
VINCRISTINE IV (1 mg TD at D1)
PREDNISONE PO (40 mg/m² from D1 to D5)
RITUXIMAB SC* (1400 mg TD at D1)
*The first cycle of rituximab is delivered by IV at the dose of 375 mg/m2

Reporting group title	R2-minichop

Reporting group description:

Experimental Arm : All patients will be treated with R2-miniCHOP at a three-weeks interval for 6 cycles

CYCLOPHOSPHAMIDE IV (400 mg/m² at D
DOXORUBICINE IV (25 mg/m² at D1)
VINCRISTINE IV (1 mg TD at D1)
PREDNISONE PO (40 mg/m² from D1 to D5)
RITUXIMAB SC* (1400 mg TD at D1)
LENALIDOMIDE PO** (10 mg TD from D1 to D14)

Reporting group title	R-mini chop

Reporting group description:

Standard Arm : All patients will be treated with R-miniCHOP at a three-weeks interval for 6 cycles

CYCLOPHOSPHAMIDE IV (400 mg/m² at D1)
DOXORUBICINE IV (25 mg/m² at D1)
VINCRISTINE IV (1 mg TD at D1)
PREDNISONE PO (40 mg/m² from D1 to D5)
RITUXIMAB SC* (1400 mg TD at D1)
*The first cycle of rituximab is delivered by IV at the dose of 375 mg/m2

Reporting group title	R2-minichop

Reporting group description:

Experimental Arm : All patients will be treated with R2-miniCHOP at a three-weeks interval for 6 cycles

CYCLOPHOSPHAMIDE IV (400 mg/m² at D
DOXORUBICINE IV (25 mg/m² at D1)
VINCRISTINE IV (1 mg TD at D1)
PREDNISONE PO (40 mg/m² from D1 to D5)
RITUXIMAB SC* (1400 mg TD at D1)
LENALIDOMIDE PO** (10 mg TD from D1 to D14)

Primary: Overall Survival

End point title	Overall Survival

End point description:

compare the efficacy of R2-miniCHOP (Sub-cutaneous Rituximab-miniCHOP + lenalidomide) and R-miniCHOP ((Sub-cutaneous Rituximab-miniCHOP).

OS will be measured from randomization to the date of death from any cause. Patients who withdraw consent for the study is considered censored at the time of withdrawal. Alive patients will be censored at their last contact.

End point type	Primary

End point timeframe:

0, 6, 12, 24 .. every 6 months

End point values	R-mini chop	R2-minichop		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	122		
Units: Months				
median (inter-quartile range (Q1-Q3))	43.5 (0.3 to 51.1)	0 (0 to 48.5)		

Statistical analyses

Statistical analysis title	Comparison of Overall survival

Statistical analysis description:

Treatment with R2-miniCHOP will be declared superior if the one-sided p-value from unstratified log-rank
test is < 0.05. Hazard ratio with two-sided 95% confidence intervals will be estimated using the Cox proportional hazards model if proportional hazard assumption holds. Graphical display of Kaplan-Meier curves will be provided to aid data interpretation visually

Comparison groups	R-mini chop v R2-minichop
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.98
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.996
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.509

Notes:

[1] - A one-sided log-rank test will be used for testing the difference in overall survival between the two treatment groups. The significance level for the primary analysis will be 0.05.
The hypothesis will be:
H0: OS (R2-miniCHOP) = OS (R--miniCHOP)
Versus
HA: OS (R2-miniCHOP) ≥ OS (R-miniCHOP)
Where OS denotes the survival distribution of the parameter time to overall survival.
For secondary parameters, statistical tests will be two-sided and performed using a 5% level of significance

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the date of informed consent signature to 30 days after last drug administration	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	3

Reporting groups	
Reporting group title	R-miniChop
Reporting group description: Standard arm	
Reporting group title	R2 minichop
Reporting group description: Experimental Arm	

Serious adverse events	R-miniChop	R2 minichop	
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 124 (61.29%)	54 / 117 (46.15%)	
number of deaths (all causes)	42	43	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
subjects affected / exposed	10 / 124 (8.06%)	12 / 117 (10.26%)	
occurrences causally related to treatment / all	3 / 11	12 / 12	
deaths causally related to treatment / all	1 / 2	7 / 7	
Vascular disorders			
VASCULAR DISORDERS			
subjects affected / exposed	2 / 124 (1.61%)	3 / 117 (2.56%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES			
subjects affected / exposed	1 / 124 (0.81%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
subjects affected / exposed	6 / 124 (4.84%)	8 / 117 (6.84%)	
occurrences causally related to treatment / all	5 / 7	8 / 9	
deaths causally related to treatment / all	1 / 2	1 / 1	
Reproductive system and breast disorders			
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
subjects affected / exposed	1 / 124 (0.81%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	4 / 124 (3.23%)	13 / 117 (11.11%)	
occurrences causally related to treatment / all	4 / 5	16 / 18	
deaths causally related to treatment / all	1 / 2	0 / 0	
Psychiatric disorders			
PSYCHIATRIC DISORDERS			
subjects affected / exposed	2 / 124 (1.61%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 124 (0.81%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
subjects affected / exposed	3 / 124 (2.42%)	7 / 117 (5.98%)	
occurrences causally related to treatment / all	1 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac disorder			

subjects affected / exposed	4 / 124 (3.23%)	6 / 117 (5.13%)	
occurrences causally related to treatment / all	3 / 4	4 / 7	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
NERVOUS SYSTEM DISORDERS			
subjects affected / exposed	2 / 124 (1.61%)	3 / 117 (2.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
subjects affected / exposed	2 / 124 (1.61%)	6 / 117 (5.13%)	
occurrences causally related to treatment / all	4 / 4	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
EYE DISORDERS			
subjects affected / exposed	0 / 124 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
GASTROINTESTINAL DISORDERS			
subjects affected / exposed	8 / 124 (6.45%)	6 / 117 (5.13%)	
occurrences causally related to treatment / all	2 / 11	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS			
subjects affected / exposed	1 / 124 (0.81%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
subjects affected / exposed	0 / 124 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

RENAL AND URINARY DISORDERS			
subjects affected / exposed	2 / 124 (1.61%)	4 / 117 (3.42%)	
occurrences causally related to treatment / all	0 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
ENDOCRINE DISORDERS			
subjects affected / exposed	1 / 124 (0.81%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
subjects affected / exposed	1 / 124 (0.81%)	5 / 117 (4.27%)	
occurrences causally related to treatment / all	0 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
INFECTIONS AND INFESTATIONS			
subjects affected / exposed	12 / 124 (9.68%)	17 / 117 (14.53%)	
occurrences causally related to treatment / all	12 / 16	20 / 21	
deaths causally related to treatment / all	1 / 2	0 / 0	
Metabolism and nutrition disorders			
METABOLISM AND NUTRITION DISORDERS			
subjects affected / exposed	2 / 124 (1.61%)	4 / 117 (3.42%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	R-miniChop	R2 minichop	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 124 (70.16%)	101 / 117 (86.32%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			

subjects affected / exposed	10 / 124 (8.06%)	12 / 117 (10.26%)	
occurrences (all)	11	12	
Vascular disorders			
VASCULAR DISORDERS			
subjects affected / exposed	3 / 124 (2.42%)	7 / 117 (5.98%)	
occurrences (all)	3	7	
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES			
subjects affected / exposed	1 / 124 (0.81%)	1 / 117 (0.85%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
subjects affected / exposed	9 / 124 (7.26%)	13 / 117 (11.11%)	
occurrences (all)	10	15	
Reproductive system and breast disorders			
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
subjects affected / exposed	1 / 124 (0.81%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	8 / 124 (6.45%)	16 / 117 (13.68%)	
occurrences (all)	11	21	
Psychiatric disorders			
PSYCHIATRIC DISORDERS			
subjects affected / exposed	2 / 124 (1.61%)	1 / 117 (0.85%)	
occurrences (all)	2	2	
Product issues			
PRODUCT ISSUES			
subjects affected / exposed	1 / 124 (0.81%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Investigations			
INVESTIGATIONS			
subjects affected / exposed	24 / 124 (19.35%)	21 / 117 (17.95%)	
occurrences (all)	49	67	
Injury, poisoning and procedural			

complications INJURY, POISONING AND PROCEDURAL COMPLICATIONS subjects affected / exposed occurrences (all)	5 / 124 (4.03%) 5	10 / 117 (8.55%) 10	
Cardiac disorders CARDIAC DISORDERS subjects affected / exposed occurrences (all)	4 / 124 (3.23%) 4	8 / 117 (6.84%) 9	
Nervous system disorders NERVOUS SYSTEM DISORDERS subjects affected / exposed occurrences (all)	7 / 124 (5.65%) 7	7 / 117 (5.98%) 7	
Blood and lymphatic system disorders BLOOD AND LYMPHATIC SYSTEM DISORDERS subjects affected / exposed occurrences (all)	36 / 124 (29.03%) 100	61 / 117 (52.14%) 147	
Eye disorders EYE DISORDERS subjects affected / exposed occurrences (all)	0 / 124 (0.00%) 0	1 / 117 (0.85%) 1	
Gastrointestinal disorders GASTROINTESTINAL DISORDERS subjects affected / exposed occurrences (all)	9 / 124 (7.26%) 12	10 / 117 (8.55%) 13	
Hepatobiliary disorders HEPATOBILIARY DISORDERS subjects affected / exposed occurrences (all)	1 / 124 (0.81%) 1	2 / 117 (1.71%) 3	
Skin and subcutaneous tissue disorders SKIN AND SUBCUTANEOUS TISSUE DISORDERS subjects affected / exposed occurrences (all)	0 / 124 (0.00%) 0	2 / 117 (1.71%) 3	
Renal and urinary disorders RENAL AND URINARY DISORDERS subjects affected / exposed occurrences (all)	3 / 124 (2.42%) 5	6 / 117 (5.13%) 6	
Endocrine disorders			

ENDOCRINE DISORDERS subjects affected / exposed occurrences (all)	1 / 124 (0.81%) 1	0 / 117 (0.00%) 0	
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS subjects affected / exposed occurrences (all)	4 / 124 (3.23%) 4	6 / 117 (5.13%) 6	
Infections and infestations INFECTIONS AND INFESTATIONS subjects affected / exposed occurrences (all)	40 / 124 (32.26%) 56	35 / 117 (29.91%) 50	
Metabolism and nutrition disorders METABOLISM AND NUTRITION DISORDERSMETABOLISM AND NUTRITION DISORDERS subjects affected / exposed occurrences (all)	11 / 124 (8.87%) 11	11 / 117 (9.40%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2014	Actualization of SAE declarations rules.
11 December 2015	Precision regarding baseline examination, bone marrow aspirate was highly recommended to exclude underlying myelodysplasia and mandatory in case of unexplained cytopenia
31 October 2016	Precision to allow inclusion of patient with chronic Hepatitis B and specific surveillance of these patients to avoid risks of virus reactivation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33444079