Clinical trial results:
PHASE II STUDY OF MINI-CHOP PLUS OFATUMUMAB (O) IN NON PREVIOULSY TREATED PATIENTS AGED OVER 80 YEARS WITH CD 20+ DIFFUSE LARGE B-CELL LYMPHOMA

Summary

EudraCT number	2009-017995-26
Trial protocol	FR BE PT
Global end of trial date	15 April 2014

Results information

Result version number	v1 (current)
This version publication date	17 March 2018
First version publication date	17 March 2018

Trial information

Trial identification

Sponsor protocol code	LNH09-7B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01195714
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	CHU Lyon Sud - Pav 6D, Pierre Bénite cedex, France, 69495
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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	06 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2014
Global end of trial reached?	Yes
Global end of trial date	15 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of O-miniCHOP in patients aged over 80 years with not previously treated CD20+ diffuse large B-cell lymphoma as measured by the overall survival (OS).

Protection of trial subjects:

Standard in oncology

Background therapy:

mini-CHOP

Evidence for comparator: -

Actual start date of recruitment	02 June 2010
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	Belgium: 14
Country: Number of subjects enrolled	France: 106
Worldwide total number of subjects	120
EEA total number of subjects	120

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	75
85 years and over	45

Subject disposition

Recruitment

Recruitment details:

First patient was included in June 2010. 106 patients were included in France, 14 in Belgium and no patient was inluded in Portugal. The last patient was included in November 2011.

Pre-assignment

Screening details:

Patients must have a Performance status 0, 1 or 2 and may receive vincristine and prednisone to improve it

Pre-assignment period milestones

Number of subjects started	120
Number of subjects completed	120

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental

Arm description:

2x3 cycles of O-miniCHOP21

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

Dosage and administration details:

1000 mg on D1 of each cycle

Number of subjects in period 1	Experimental
Started	120
Induction	115
Consolidation	98
Completed	89
Not completed	31
Consent withdrawn by subject	6
Physician decision	2
Adverse event, non-fatal	6
Exclusion criterion	2

DEATH	2
comorbidities	5
Protocol deviation	2
Lack of efficacy	6

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
Patient with PS 0, 1 or 2	

Reporting group values	Treatment	Total	
Number of subjects	120	120	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	83.9		
standard deviation	± 3.38	-	
Gender categorical Units: Subjects			
Female	55	55	
Male	65	65	

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
the Full Analysis Set (FAS) corresponds to patients enrolled in the study and having signed the informed consent, regardless of whether they have received study treatment or not	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
the PP set corresponds to patients enrolled in the study with no major protocol deviations	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
the safety set corresponds to patients who have received at least one dose of treatment regimen, including prephase.	

Reporting group values	FAS	PP	Safety set
Number of subjects	120	115	120
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	83.9	84.1	83.9
standard deviation	± 3.38	± 3.34	± 3.38
Gender categorical Units: Subjects			
Female	55	54	55
Male	65	61	65

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: 2x3 cycles of O-miniCHOP21	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: the Full Analysis Set (FAS) corresponds to patients enrolled in the study and having signed the informed consent, regardless of whether they have received study treatment or not	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description: the PP set corresponds to patients enrolled in the study with no major protocol deviations	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: the safety set corresponds to patients who have received at least one dose of treatment regimen, including prephase.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]
End point description: measured from the date of inclusion to the date of death from any cause. Patients who have not died at the time of the analysis or who are lost to follow-up are censored at the date of last contact.	
End point type	Primary
End point timeframe: 2 YEARS	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since there is only one treatment arm, it is not possible to indicate comparative statistical analysis as required by EudraCT system

End point values	FAS	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	115		
Units: percent				
arithmetic mean (confidence interval 95%)	64.7 (55.3 to 72.7)	65.0 (55.3 to 73.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

measured from the date of inclusion to the date of first documented disease progression, relapse or death from any cause, whichever occurs first. Patients alive and free of progression and patients who are lost to follow-up are censored at their last tumor assessment date.

End point type	Secondary

End point timeframe:

2 YEARS

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: percent				
arithmetic mean (confidence interval 95%)	57.2 (47.7 to 65.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival (EFS)

End point title	Event Free Survival (EFS)

End point description:

measured from the date of randomization to the date of first documented disease progression, relapse, initiation of new anti-lymphoma therapy or death from any cause. Patients alive and free of event or who are lost to follow up are censored at their last tumor assessment date.

End point type	Secondary

End point timeframe:

2 YEARS

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: percent				
arithmetic mean (confidence interval 95%)	53.1 (43.7 to 61.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Free Survival (DFS)

End point title	Disease Free Survival (DFS)

End point description:

measured from the time of attainment of CR, CRu or PR to the date of first documented disease progression, relapse or death as a result of lymphoma or acute toxicity of treatment. Patients alive and free of progression are censored at their last follow-up date.
Death from a secondary cancer or from unknown cause are considered as an event. Unrelated death is defined as death from a cause not related to the lymphoma, any examination done for the lymphoma, or any treatment of the lymphoma.

End point type	Secondary

End point timeframe:

2 YEARS

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: percent				
arithmetic mean (confidence interval 95%)	66.6 (54.0 to 76.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

measured from the time of attainment of CR/CRu or PR to the date of first documented disease progression, relapse or death from any cause. Patients alive and free of progression are censored at their last follow-up date.

End point type	Secondary

End point timeframe:

2 YEARS

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: percent				
arithmetic mean (confidence interval 95%)	63.0 (52.1 to 72.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response / Uncertain Complete Response (CR/CRu)

End point title	Complete Response / Uncertain Complete Response (CR/CRu)

End point description:

Patients without response assessment (due to whatever reason) are considered as non-responder.

End point type	Secondary

End point timeframe:

END OF TREATMENT

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: percent				
arithmetic mean (confidence interval 95%)	55.8 (46.5 to 64.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

End point type	Secondary

End point timeframe:

END OF TREATMENT

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: percent				
arithmetic mean (confidence interval 95%)	67.5 (58.3 to 75.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

until 90 days after the last study drug administration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	NK

Reporting groups

Reporting group title	SAFETY SET

Reporting group description: -

Serious adverse events	SAFETY SET		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 120 (35.83%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Benign bone neoplasm			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Haematoma				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Device dislocation				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Cytokine release syndrome				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract congestion			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Depression			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull fractured base			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Aortic valve stenosis				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial fibrillation				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracardiac thrombus				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Paraplegia				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parkinson's disease				

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bone marrow failure			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Ulcerative keratitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal strangulated hernia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Bladder obstruction			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Urinary retention			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Klebsiella infection			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SAFETY SET		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 120 (70.83%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Noeplan benign, malignant and unspecified			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Vascular disorders			
Vascular Disorders			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	10		
General disorders and administration site conditions			
General DIsorders and Administration site conditions			
subjects affected / exposed	13 / 120 (10.83%)		
occurrences (all)	13		
Immune system disorders			
Immune System Disorders			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Social circumstances			
Social circumstances			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Reproductive system disorders			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Respiratory, Thoracic and Mediastinal Disorders			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	8		
Psychiatric disorders			
Psychiatric Disorders			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	5		

Investigations Investigations subjects affected / exposed occurrences (all)	 12 / 120 (10.00%) 24		
Injury, poisoning and procedural complications Injury , Poisoning and Procedural complications subjects affected / exposed occurrences (all)	 17 / 120 (14.17%) 19		
Cardiac disorders Cardiac Disorders subjects affected / exposed occurrences (all)	 8 / 120 (6.67%) 10		
Nervous system disorders Nervous System Disorders subjects affected / exposed occurrences (all)	 13 / 120 (10.83%) 13		
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	 37 / 120 (30.83%) 110		
Ear and labyrinth disorders Ear and Labyrinth disorders subjects affected / exposed occurrences (all)	 1 / 120 (0.83%) 1		
Eye disorders Eye Disorders subjects affected / exposed occurrences (all)	 2 / 120 (1.67%) 3		
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	 9 / 120 (7.50%) 11		
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	 9 / 120 (7.50%) 9		
Renal and urinary disorders			

Renal and urinary Disorders subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 4		
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Musculoskeletal and connective tissue disorders Muskuloskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2		
Infections and infestations Infections and Infestations subjects affected / exposed occurrences (all)	29 / 120 (24.17%) 46		
Metabolism and nutrition disorders Metabolism and Nutrition Disorders subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2010	Addition of the Charlson score which is a comorbidity index to recover at the time the patient enters the trial
30 May 2011	IB modification : change in expected adverse events
27 February 2013	1. Addition of a neurological examination during clinical examinations 2. Indications on what to do in case of PML suspicion 3. Further information on expected toxicities 4. Investigator's Brochure update
15 April 2013	IB update : risk of toxic epidermal necrolysis in FL

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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