



## Clinical trial results:

**A multicentre, phase III, open-label, randomized study in patients with advanced follicular lymphoma evaluating the benefit of maintenance therapy with rituximab (Mabthéra®) after induction of response with chemotherapy plus rituximab in comparison with no maintenance therapy.**

### Summary

EudraCT number	2004-001756-36
Trial protocol	DK FI CZ PT GB ES BE
Global end of trial date	31 December 2016

### Results information

Result version number	v1 (current)
This version publication date	29 September 2018
First version publication date	29 September 2018

### Trial information

#### Trial identification

Sponsor protocol code	MO18264
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	LYSA
Sponsor organisation address	CH Lyon Sud - Service d'Hématologie - Bâtiment 1F - 3ème étage, Pierre Bénite, 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	31 December 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the benefit of maintenance therapy with rituximab as measured by progression-free survival (PFS) in comparison with no maintenance therapy after induction of response with chemotherapy plus rituximab in patients with high tumor burden follicular lymphoma

Protection of trial subjects:

New anti-lymphoma treatment is defined as any radiation therapy (even local), chemotherapy or immunotherapy, either alone or in combination. Any new, non-protocol anti-lymphoma treatment will be considered as an event for purposes of EFS assessment.

New anti-lymphoma treatment should be considered:

- if a patient does demonstrate disease progression during induction treatment;
- at the discretion of the physician if a patient does not reach at least a partial response or a complete (either confirmed or unconfirmed) at the end of the induction treatment;
- during the maintenance phase, for patients in both arms (rituximab maintenance or observation), at any time of documented disease progression if this progression is symptomatic and/or if the physician considers that a new treatment is necessary for patients benefit.
- during the follow-up period, at any time of documented disease progression if this progression is symptomatic and/or if the physician considers that a new treatment is necessary for patients benefit.

Background therapy:

The standard treatments used in this study are:

- CHOP:

Cyclophosphamide 750 mg/m<sup>2</sup> day 1

Doxorubicin 50 mg/m<sup>2</sup> day 1

Vincristine 1.4 mg/m<sup>2</sup> (2 mg cap) day 1

Prednisone 100 mg/day (× 5 days)

- CVP:

Cyclophosphamide 750 mg/m<sup>2</sup> day 1

Vincristine 1.4 mg/m<sup>2</sup> (2 mg cap) day 1

Prednisone 40 mg/m<sup>2</sup> (× 5 days)

- FCM:

Fludarabine 25 mg/m<sup>2</sup> (× 3 days)

Cyclophosphamide 200 mg/m<sup>2</sup> (× 3 days)

Mitoxantrone 6 mg/m<sup>2</sup> day 1

Evidence for comparator: -

Actual start date of recruitment	24 December 2004
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: 16
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Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Belgium: 75
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	Denmark: 48
Country: Number of subjects enrolled	Finland: 24
Country: Number of subjects enrolled	France: 624
Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Australia: 132
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	China: 8
Country: Number of subjects enrolled	Colombia: 11
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	India: 14
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	New Zealand: 26
Country: Number of subjects enrolled	Peru: 10
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Thailand: 18
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Uruguay: 3
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 9
Worldwide total number of subjects	1202
EEA total number of subjects	918

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)	919
From 65 to 84 years	282
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

Be17/03/05  
Fr24/12/04  
UK06/07/06  
Argent07/10/05  
Aus01/07/05  
NZ24/08/05  
Brazil31/03/06  
China09/05/06  
Colombia03/08/05  
Croatia30/12/05  
Dmark31/05/05  
Spa15/07/05  
Finl 03/01/06  
India21/10/05  
Israel 25/04/06  
NL 06/03/06  
Peru 17/11/05  
Portu 17/11/05  
CZ 24/11/05  
Serb 08/02/06  
Thai 20/10/05  
Turkey 30/11/05  
Urug12/07/06  
Venez 16/01/06

### Pre-assignment

Screening details:

ICF, Medical history, examination, Height, weight, BSA, B-Symptoms, ECOG, Ann Arbor Staging, Spleen and Liver evaluation, haematology, biochemistry, Serum immunoglobulins, Pregnancy test, echocardiography or left VEF, CT-SCAN, Tumor lesion measurements, BOM, QoL, tumor biopsy and serum samples for additional studies.  
1202 included, 1022 randomized

### Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	No
Arm title	Rituximab

Arm description:

R-CHOP 6 cycles of 21 days during induction period:  
Rituximab 375 mg/ m2  
Cyclophosphamide 750 mg/m2 day 1  
Doxorubicin 50 mg/m2 day 1  
Vincristine 1.4 mg/m2 (2 mg cap) day 1

R-CVP 8 cycles of 21 days during induction period:  
Rituximab 375 mg/ m2  
Cyclophosphamide 750 mg/m2 day 1  
Vincristine 1.4 mg/m2 (2 mg cap) day 1  
Prednisone 40 mg/m2 (× 5 days)  
Prednisone 100 mg/day (× 5 days)

R-FCM 6 cycles of 28 days during induction period:  
Rituximab 375 mg/ m2  
Fludarabine 25 mg/m2 (× 3 days)  
Cyclophosphamide 200 mg/m2 (× 3 days)

Mitoxantrone 6 mg/m<sup>2</sup> day 1

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	R
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dilution of 2mG/mL

Induction period:

Patients will receive 375 mg/m<sup>2</sup> rituximab, administered by IV infusion, at each Day 1 of each cycle (6 or 8 cycles)

+ 2 additional rituximab infusions for R-CHOP (cycle 7 and 8) and R-FCM (day 15 of cycle 1 and cycle 4)

Maintenance period:

Patients will receive 375 mg/m<sup>2</sup> rituximab, administered by IV infusion every 8 weeks starting 8 weeks  $\pm$  7 days after the last induction treatment

every 8 weeks for a total of 12 cycles (2 years) or observation (without rituximab) for 2 years

<b>Arm title</b>	observation
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Arm description: -

Arm type	No intervention
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No investigational medicinal product assigned in this arm

<b>Number of subjects in period 1</b>	Rituximab	observation
Started	596	606
Completed	501	508
Not completed	95	98
Adverse event, serious fatal	1	-
Adverse event, non-fatal	4	5
Non evaluable patients	90	-
non evaluable	-	93

## Period 2

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

## Arms

Are arms mutually exclusive?	No
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<b>Arm title</b>	Observation
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Rituximab
Arm description:	
R-CHOP 6 cycles of 21 days + 2 additional R cycles 7 and 8	
or R-CVP 8 cycles of 21 days	
or R-FCM 6 cycles of 28 days + 2 additional R on D15 of cycles 1 and 4	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	R
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Dosage: 375mg/m <sup>2</sup>	
dilution of 2mg/mL	

<b>Number of subjects in period 2</b>	Observation	Rituximab
Started	513	506
Completed	508	501
Not completed	5	5
Adverse event, serious fatal	-	1
Adverse event, non-fatal	5	4

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline period
Reporting group description: -	

Reporting group values	Baseline period	Total	
Number of subjects	1202	1202	
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			
A similar proportion of male and female patients were randomized to the maintenance/observation phase (52% vs 48%, respectively), and the study arms were well balanced with respect to gender. The median age of patients at randomization to the maintenance/observation phase was 57.0 years (range, 23-85 years). The study arms were also balanced in terms of other baseline characteristics such as height, weight, and body surface area.			
Units: years			
median	57		
full range (min-max)	23 to 85	-	
Gender categorical			
Units: Subjects			
Female	577	577	
Male	625	625	

## End points

### End points reporting groups

Reporting group title	Rituximab
Reporting group description:	
R-CHOP 6 cycles of 21 days during induction period:	
Rituximab 375 mg/ m <sup>2</sup>	
Cyclophosphamide 750 mg/m <sup>2</sup> day 1	
Doxorubicin 50 mg/m <sup>2</sup> day 1	
Vincristine 1.4 mg/m <sup>2</sup> (2 mg cap) day 1	
R-CVP 8 cycles of 21 days during induction period:	
Rituximab 375 mg/ m <sup>2</sup>	
Cyclophosphamide 750 mg/m <sup>2</sup> day 1	
Vincristine 1.4 mg/m <sup>2</sup> (2 mg cap) day 1	
Prednisone 40 mg/m <sup>2</sup> (× 5 days)	
Prednisone 100 mg/day (× 5 days)	
R-FCM 6 cycles of 28 days during induction period:	
Rituximab 375 mg/ m <sup>2</sup>	
Fludarabine 25 mg/m <sup>2</sup> (× 3 days)	
Cyclophosphamide 200 mg/m <sup>2</sup> (× 3 days)	
Mitoxantrone 6 mg/m <sup>2</sup> day 1	
Reporting group title	observation
Reporting group description: -	
Reporting group title	Observation
Reporting group description: -	
Reporting group title	Rituximab
Reporting group description:	
R-CHOP 6 cycles of 21 days + 2 additional R cycles 7 and 8	
or R-CVP 8 cycles of 21 days	
or R-FCM 6 cycles of 28 days + 2 additional R on D15 of cycles 1 and 4	

### Primary: Progression free survival

End point title	Progression free survival
End point description:	
End point type	Primary
End point timeframe:	
two years from randomization	

End point values	Observation	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	513	506		
Units: median				
median (confidence interval 95%)	4.06 (3.45 to 4.67)	10.49 (9.88 to 11.1)		

## Statistical analyses

<b>Statistical analysis title</b>	Progression Free Survival
Comparison groups	Rituximab v Observation
Number of subjects included in analysis	1019
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[1]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.73
Variability estimate	Standard deviation

Notes:

[1] - Stratified

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During induction treatment, adverse events will be recorded until 30 days after the administration of the last treatment dose. During the maintenance phase, adverse events will be recorded until 6 months after the administration of the last treatment dose

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	1

### Reporting groups

Reporting group title	Observation
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Reporting group description:

AE description in the observation arm

Reporting group title	Rituximab
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Reporting group description:

AE description on the rituximab arm

Serious adverse events	Observation	Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 508 (13.39%)	106 / 501 (21.16%)	
number of deaths (all causes)	83	84	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer			
subjects affected / exposed	21 / 508 (4.13%)	22 / 501 (4.39%)	
occurrences causally related to treatment / all	0 / 21	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular			
subjects affected / exposed	2 / 508 (0.39%)	3 / 501 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical			
subjects affected / exposed	1 / 508 (0.20%)	2 / 501 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pregnancy, puerperium and perinatal conditions Pregnancy			
	subjects affected / exposed	3 / 508 (0.59%)	4 / 501 (0.80%)
	occurrences causally related to treatment / all	0 / 4	0 / 4
	deaths causally related to treatment / all	0 / 0	0 / 0
General disorders and administration site conditions General disorders			
	subjects affected / exposed	4 / 508 (0.79%)	4 / 501 (0.80%)
	occurrences causally related to treatment / all	0 / 5	0 / 4
	deaths causally related to treatment / all	0 / 0	0 / 2
Social circumstances Social			
	subjects affected / exposed	0 / 508 (0.00%)	1 / 501 (0.20%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Reproductive system and breast disorders Reproductive			
	subjects affected / exposed	0 / 508 (0.00%)	1 / 501 (0.20%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders Respiratory			
	subjects affected / exposed	1 / 508 (0.20%)	4 / 501 (0.80%)
	occurrences causally related to treatment / all	0 / 1	0 / 4
	deaths causally related to treatment / all	0 / 0	0 / 0
Psychiatric disorders Psychiatric			
	subjects affected / exposed	6 / 508 (1.18%)	5 / 501 (1.00%)
	occurrences causally related to treatment / all	0 / 6	0 / 5
	deaths causally related to treatment / all	0 / 0	0 / 0
Product issues Product			

subjects affected / exposed	0 / 508 (0.00%)	1 / 501 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	9 / 508 (1.77%)	3 / 501 (0.60%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac			
subjects affected / exposed	2 / 508 (0.39%)	13 / 501 (2.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system			
subjects affected / exposed	9 / 508 (1.77%)	10 / 501 (2.00%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood			
subjects affected / exposed	2 / 508 (0.39%)	2 / 501 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear			
subjects affected / exposed	1 / 508 (0.20%)	1 / 501 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye			
subjects affected / exposed	1 / 508 (0.20%)	3 / 501 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal			

subjects affected / exposed	3 / 508 (0.59%)	10 / 501 (2.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hepatobiliary disorders</b>			
Liver			
subjects affected / exposed	1 / 508 (0.20%)	2 / 501 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
Kidney			
subjects affected / exposed	3 / 508 (0.59%)	3 / 501 (0.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Endocrine disorders</b>			
Endocrine			
subjects affected / exposed	0 / 508 (0.00%)	1 / 501 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Muscles and tissue			
subjects affected / exposed	3 / 508 (0.59%)	6 / 501 (1.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Infections			
subjects affected / exposed	6 / 508 (1.18%)	26 / 501 (5.19%)	
occurrences causally related to treatment / all	0 / 6	0 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Observation	Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	194 / 508 (38.19%)	285 / 501 (56.89%)	

Neoplasms benign, malignant and unspecified (incl cysts and polyps) Cancers subjects affected / exposed occurrences (all)	23 / 508 (4.53%) 23	24 / 501 (4.79%) 28	
Vascular disorders Vascular subjects affected / exposed occurrences (all)	6 / 508 (1.18%) 6	6 / 501 (1.20%) 6	
Surgical and medical procedures Surgical subjects affected / exposed occurrences (all)	1 / 508 (0.20%) 1	5 / 501 (1.00%) 5	
Pregnancy, puerperium and perinatal conditions Pregnancy subjects affected / exposed occurrences (all)	3 / 508 (0.59%) 3	4 / 501 (0.80%) 4	
General disorders and administration site conditions General disorders subjects affected / exposed occurrences (all)	9 / 508 (1.77%) 10	10 / 501 (2.00%) 10	
Immune system disorders Immune subjects affected / exposed occurrences (all)	1 / 508 (0.20%) 1	1 / 501 (0.20%) 1	
Social circumstances Social subjects affected / exposed occurrences (all)	0 / 508 (0.00%) 0	1 / 501 (0.20%) 1	
Reproductive system and breast disorders Reproductive subjects affected / exposed occurrences (all)	2 / 508 (0.39%) 2	4 / 501 (0.80%) 4	
Respiratory, thoracic and mediastinal disorders Respiratory subjects affected / exposed occurrences (all)	4 / 508 (0.79%) 5	16 / 501 (3.19%) 16	

Psychiatric disorders Psychiatric subjects affected / exposed occurrences (all)	6 / 508 (1.18%) 6	6 / 501 (1.20%) 6	
Product issues Products subjects affected / exposed occurrences (all)	0 / 508 (0.00%) 0	1 / 501 (0.20%) 1	
Hepatobiliary disorders Liver subjects affected / exposed occurrences (all)	1 / 508 (0.20%) 1	4 / 501 (0.80%) 4	
Investigations Investigations subjects affected / exposed occurrences (all)	5 / 508 (0.98%) 5	5 / 501 (1.00%) 5	
Injury, poisoning and procedural complications Injury subjects affected / exposed occurrences (all)	10 / 508 (1.97%) 10	5 / 501 (1.00%) 5	
Cardiac disorders Cardiac subjects affected / exposed occurrences (all)	6 / 508 (1.18%) 6	17 / 501 (3.39%) 18	
Nervous system disorders Nervous system subjects affected / exposed occurrences (all)	13 / 508 (2.56%) 13	14 / 501 (2.79%) 14	
Blood and lymphatic system disorders Blood subjects affected / exposed occurrences (all)	8 / 508 (1.57%) 11	27 / 501 (5.39%) 35	
Ear and labyrinth disorders Ear subjects affected / exposed occurrences (all)	1 / 508 (0.20%) 1	1 / 501 (0.20%) 1	
Eye disorders			

Eye subjects affected / exposed occurrences (all)	3 / 508 (0.59%) 3	3 / 501 (0.60%) 3	
Gastrointestinal disorders Gastrointestinal subjects affected / exposed occurrences (all)	6 / 508 (1.18%) 7	12 / 501 (2.40%) 13	
Skin and subcutaneous tissue disorders Skin subjects affected / exposed occurrences (all)	3 / 508 (0.59%) 3	3 / 501 (0.60%) 3	
Renal and urinary disorders Kidney subjects affected / exposed occurrences (all)	3 / 508 (0.59%) 3	5 / 501 (1.00%) 5	
Endocrine disorders Endocrine subjects affected / exposed occurrences (all)	1 / 508 (0.20%) 1	2 / 501 (0.40%) 2	
Musculoskeletal and connective tissue disorders Muscles subjects affected / exposed occurrences (all)	9 / 508 (1.77%) 9	10 / 501 (2.00%) 11	
Infections and infestations Infections subjects affected / exposed occurrences (all)	125 / 508 (24.61%) 167	200 / 501 (39.92%) 305	
Metabolism and nutrition disorders Metabolism subjects affected / exposed occurrences (all)	4 / 508 (0.79%) 4	4 / 501 (0.80%) 4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2006	Extension of the number of recruited patients to 900
17 June 2006	Canceling of the first interim analysis after 50% of events (= 172 events)
26 September 2006	Modification of the primary criterion and increase of recruited patient from 900 to 1200
15 October 2013	Extension of the study regarding patients until December 2016

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/21176949>