Clinical trial results:
A RANDOMIZED PHASE III STUDY USING A PET-DRIVEN STRATEGY AND COMPARING GA101 OR RITUXIMAB IN COMBINATION WITH A CHEMOTHERAPY DELIVERED EVERY 14 DAYS (ACVBP OR CHOP) IN DLBCL CD20+ LYMPHOMA UNTREATED PATIENTS FROM 18 TO 60 PRESENTING WITH 1 OR MORE ADVERSE PROGNOSTIC FACTORS OF THE AGE-ADJUSTED IPI

Summary

EudraCT number	2011-005851-15
Trial protocol	BE
Global end of trial date	31 December 2017

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	GAINED

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01659099
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	CH LYON SUD BATIMENT 2D, PIERRE BENITE, France, 69495
Public contact	Project Management, LYSARC, 33 472669333, gained@lysarc.org
Scientific contact	Coordinating investigator, Pr Steven Le Gouill, 33 240083271, gained@lysarc.org

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 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate an improvement of the 2-year Event Free Survival (EFS) in DLBCL CD20+ patients aged from 18 to 60 years with 1 to 3 adverse prognostic factors of the aa-IPI treated with GA101 or Rituximab in combination with ACVBP14 or CHOP14 in a PET-driven strategy.

Protection of trial subjects:

DSMC

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 September 2012
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: 40
Country: Number of subjects enrolled	France: 630
Worldwide total number of subjects	670
EEA total number of subjects	670

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)	670
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From September 20, 2012, to July 30, 2015,
France
Belgium

Pre-assignment

Screening details:

Patients provided informed consent before any non-routine screening tests or evaluations were conducted. The inclusion and exclusion criteria were assessed during the screening period. Patients must have continued to meet all eligibility criteria on day 1 cycle 1 of induction treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Obinutuzumab

Arm description:

Obinutuzumab + Chemo (CHOP or ACVP)

Arm type	Experimental
Investigational medicinal product name	CHOP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard use

Investigational medicinal product name	ACVBP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard use

Arm title	Rituximab

Arm description:

Rituximab + Chemo (CHOP or ACVP)

Arm type	Active comparator
Investigational medicinal product name	CHOP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: Standard use	
Investigational medicinal product name	ACVBP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Standard use	

Number of subjects in period 1	Obinutuzumab	Rituximab
Started	336	334
Completed	312	312
Not completed	24	22
Consent withdrawn by subject	-	2
Adverse event, non-fatal	8	7
Death	2	1
concurrent illness	1	1
Progression	2	1
Untreated	4	3
other	5	2
Protocol deviation	2	5

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Obinutuzumab

Arm description:

Obinutuzumab + MTX/VP/Ifosfamide/Arac/CHOP if PET 2 neg / PET 4 neg
MTX+BEAM + ASCT if PET 2 pos / PET 4 neg
Salvage therapy if PET 4 pos

Arm type	Experimental
Investigational medicinal product name	MTX/VP/Ifosfamide/Arac/CHOP/R
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
standard use

Arm title	Rituximab

Arm description:
Rituximab + MTX/VP/Ifosfamide/Arac/CHOP if PET 2 neg / PET 4 neg
MTX+BEAM + ASCT if PET 2 pos / PET 4 neg
Salvage therapy if PET 4 pos

Arm type	Active comparator
Investigational medicinal product name	MTX/VP/Ifosfamide/Arac/CHOP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
standard use

Number of subjects in period 2	Obinutuzumab	Rituximab
Started	312	312
Completed	227	197
Not completed	85	115
Consent withdrawn by subject	-	1
missing PET	20	23
Adverse event, non-fatal	15	16
concurrent illness	1	-
PET4+	37	56
Progression	-	2
other	6	11
Protocol deviation	4	6
Lack of efficacy	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Obinutuzumab
Reporting group description:	
Obinutuzumab + Chemo (CHOP or ACVP)	

Reporting group title	Rituximab
Reporting group description:	
Rituximab + Chemo (CHOP or ACVP)	

Reporting group values	Obinutuzumab	Rituximab	Total
Number of subjects	336	334	670
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			
median	49	48	
full range (min-max)	19 to 60	18 to 61	-
Gender categorical			
Units: Subjects			
Female	133	164	297
Male	203	170	373

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set included 670 patients, 336 in the GA101 arm and 334 in the Rituximab arm.	

Reporting group values	ITT		
Number of subjects	670		
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			
median	48		
full range (min-max)	18 to 61		
Gender categorical Units: Subjects			
Female	297		
Male	373		

End points

End points reporting groups

Reporting group title	Obinutuzumab
Reporting group description:	
Obinutuzumab + Chemo (CHOP or ACVP)	

Reporting group title	Rituximab
Reporting group description:	
Rituximab + Chemo (CHOP or ACVP)	
Reporting group title	Obinutuzumab
Reporting group description:	
Obinutuzumab + MTX/VP/Ifosfamide/Arac/CHOP if PET 2 neg / PET 4 neg MTX+BEAM + ASCT if PET 2 pos / PET 4 neg Salvage therapy if PET 4 pos	
Reporting group title	Rituximab
Reporting group description:	
Rituximab + MTX/VP/Ifosfamide/Arac/CHOP if PET 2 neg / PET 4 neg MTX+BEAM + ASCT if PET 2 pos / PET 4 neg Salvage therapy if PET 4 pos	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set included 670 patients, 336 in the GA101 arm and 334 in the Rituximab arm.	

Primary: EFS

End point title	EFS
End point description:	
Progression, Death, PET positivity after central review after 2 and/or 4 cycles were considered as an event	
End point type	Primary
End point timeframe:	
2y -EFS	

End point values	Obinutuzumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	197		
Units: percent of patient with no event				
number (confidence interval 95%)	59.8 (54.3 to 64.8)	56.6 (51.1 to 61.8)		

Statistical analyses

Statistical analysis title	Comparison Obinutuzumab vs Rituximab
Comparison groups	Obinutuzumab v Rituximab

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.123 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.1
Variability estimate	Standard deviation

Notes:
[1] - Stratified

Secondary: Early metabolic response rate - 2 cycles

End point title	Early metabolic response rate - 2 cycles
End point description: Central review	
End point type	Secondary
End point timeframe: 2 cycles	

End point values	Obinutuzumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	197		
Units: percent of negative PET-2				
number (not applicable)	73.5	68.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response rate Cheson 2007

End point title	Overall Response rate Cheson 2007
End point description:	
End point type	Secondary
End point timeframe: 4 cycles and end of treatment	

End point values	Obinutuzumab	Rituximab	Obinutuzumab	Rituximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	312	312	227	197
Units: percent of CR+PR				
number (confidence interval 95%)	90.1 (86.2 to 93.1)	84.2 (79.7 to 88.1)	86.2 (81.9 to 89.8)	85.3 (80.9 to 89.0)

Statistical analyses

Statistical analysis title	Comparison of ORR - 4 cycles
Comparison groups	Obinutuzumab v Rituximab
Number of subjects included in analysis	624
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.018 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Stratified on AA-IPI and chemotherapy

[3] - 4 cycles

Statistical analysis title	Comparison of ORR - End of treatment
Comparison groups	Obinutuzumab v Rituximab
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.836
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Stratified on AA-IPI and chemotherapy

Secondary: Overall Response rate Cheson 1999

End point title	Overall Response rate Cheson 1999

End point description:

End point type	Secondary

End point timeframe:

4 cycles and end of treatment

End point values	Obinutuzumab	Rituximab	Obinutuzumab	Rituximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	312	312	227	197
Units: Percent of PR+CR				
number (confidence interval 95%)	73.4 (68.1 to 78.2)	71.4 (66.0 to 76.3)	80.6 (75.8 to 84.8)	77.1 (72.1 to 81.6)

Statistical analyses

Statistical analysis title	Comparison ORR - 4 cycles
Comparison groups	Obinutuzumab v Rituximab
Number of subjects included in analysis	624
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.551 [5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - Stratified on AA-IPI and chemotherapy

Statistical analysis title	Comparison ORR - End of treatment
Comparison groups	Obinutuzumab v Rituximab
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368 [6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Stratified on AA-IPI and chemotherapy

Secondary: Duration of response

End point title	Duration of response

End point description:

End point type	Secondary

End point timeframe:

2 years

End point values	Obinutuzumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	197		
Units: percent of non event				
number (confidence interval 95%)	87.4 (83.1 to 90.7)	86.8 (82.3 to 90.2)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Rituximab v Obinutuzumab
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.984
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.652
upper limit	1.484
Variability estimate	Standard deviation

Secondary: Progression-free survival	
End point title	Progression-free survival
End point description:	
End point type	Secondary
End point timeframe:	
2 years	

End point values	Obinutuzumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	197		
Units: Percent				
number (confidence interval 95%)	83.2 (78.7 to 86.8)	83.0 (78.5 to 86.7)		

Statistical analyses

Statistical analysis title	Comparison of PFS
Comparison groups	Obinutuzumab v Rituximab
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.735
upper limit	1.436

Variability estimate	Standard deviation

Secondary: Overall survival

End point title	Overall survival
End point description:	
End point type	Secondary
End point timeframe:	
2 years	

End point values	Obinutuzumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	197		
Units: percent				
number (confidence interval 95%)	90.7 (87.0 to 93.4)	91.8 (88.1 to 94.3)		

Statistical analyses

Statistical analysis title	Comparison of OS
Comparison groups	Rituximab v Obinutuzumab
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.959
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.507
Variability estimate	Standard deviation

Secondary: Early metabolic response rate - 4 cycles

End point title	Early metabolic response rate - 4 cycles
End point description:	
Central review	
End point type	Secondary
End point timeframe:	
4 cycles	

End point values	Obinutuzumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	197		
Units: percent of negative PET-4				
number (not applicable)	87.5	80.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28 days after end of treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Obinutuzumab
Reporting group description: -	
Reporting group title	Rituximab

Reporting group description: -

Serious adverse events	Obinutuzumab	Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	142 / 336 (42.26%)	223 / 331 (67.37%)	
number of deaths (all causes)	34	36	
number of deaths resulting from adverse events	8	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
subjects affected / exposed	3 / 336 (0.89%)	6 / 331 (1.81%)	
occurrences causally related to treatment / all	2 / 3	2 / 6	
deaths causally related to treatment / all	1 / 1	1 / 1	
Vascular disorders			
VASCULAR DISORDERS			
subjects affected / exposed	2 / 336 (0.60%)	6 / 331 (1.81%)	
occurrences causally related to treatment / all	0 / 2	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES			
subjects affected / exposed	1 / 336 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
subjects affected / exposed	24 / 336 (7.14%)	25 / 331 (7.55%)	
occurrences causally related to treatment / all	25 / 33	25 / 31	
deaths causally related to treatment / all	2 / 2	0 / 0	
Immune system disorders			
IMMUNE SYSTEM DISORDERS			
subjects affected / exposed	1 / 336 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	16 / 336 (4.76%)	15 / 331 (4.53%)	
occurrences causally related to treatment / all	10 / 16	13 / 19	
deaths causally related to treatment / all	2 / 2	0 / 1	
Psychiatric disorders			
PSYCHIATRIC DISORDERS			
subjects affected / exposed	1 / 336 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
INVESTIGATIONS			
subjects affected / exposed	2 / 336 (0.60%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
subjects affected / exposed	22 / 336 (6.55%)	9 / 331 (2.72%)	
occurrences causally related to treatment / all	6 / 22	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIAC DISORDERS			

subjects affected / exposed	5 / 336 (1.49%)	5 / 331 (1.51%)	
occurrences causally related to treatment / all	1 / 5	4 / 6	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
NERVOUS SYSTEM DISORDERS			
subjects affected / exposed	4 / 336 (1.19%)	13 / 331 (3.93%)	
occurrences causally related to treatment / all	1 / 4	3 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
subjects affected / exposed	16 / 336 (4.76%)	9 / 331 (2.72%)	
occurrences causally related to treatment / all	17 / 18	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
GASTROINTESTINAL DISORDERS			
subjects affected / exposed	25 / 336 (7.44%)	22 / 331 (6.65%)	
occurrences causally related to treatment / all	20 / 30	26 / 31	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS			
subjects affected / exposed	2 / 336 (0.60%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
subjects affected / exposed	5 / 336 (1.49%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	5 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL AND URINARY DISORDERS			
subjects affected / exposed	11 / 336 (3.27%)	8 / 331 (2.42%)	
occurrences causally related to treatment / all	3 / 12	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

ENDOCRINE DISORDERS			
subjects affected / exposed	1 / 336 (0.30%)	0 / 331 (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	3 / 336 (0.89%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	2 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
INFECTIONS AND INFESTATIONS			
subjects affected / exposed	61 / 336 (18.15%)	36 / 331 (10.88%)	
occurrences causally related to treatment / all	77 / 86	37 / 46	
deaths causally related to treatment / all	1 / 2	0 / 0	
Metabolism and nutrition disorders			
METABOLISM AND NUTRITION DISORDERS			
subjects affected / exposed	6 / 336 (1.79%)	7 / 331 (2.11%)	
occurrences causally related to treatment / all	4 / 6	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Obinutuzumab	Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	325 / 336 (96.73%)	307 / 331 (92.75%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
subjects affected / exposed	3 / 336 (0.89%)	7 / 331 (2.11%)	
occurrences (all)	3	7	
Vascular disorders			
VASCULAR DISORDERS			
subjects affected / exposed	10 / 336 (2.98%)	10 / 331 (3.02%)	
occurrences (all)	11	11	
Surgical and medical procedures			

SURGICAL AND MEDICAL PROCEDURES			
subjects affected / exposed	1 / 336 (0.30%)	0 / 331 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
subjects affected / exposed	9 / 336 (2.68%)	10 / 331 (3.02%)	
occurrences (all)	10	10	
Immune system disorders			
IMMUNE SYSTEM DISORDERS			
subjects affected / exposed	3 / 336 (0.89%)	2 / 331 (0.60%)	
occurrences (all)	3	2	
Reproductive system and breast disorders			
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
subjects affected / exposed	1 / 336 (0.30%)	0 / 331 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	22 / 336 (6.55%)	27 / 331 (8.16%)	
occurrences (all)	23	39	
Psychiatric disorders			
PSYCHIATRIC DISORDERS			
subjects affected / exposed	2 / 336 (0.60%)	3 / 331 (0.91%)	
occurrences (all)	7	3	
Investigations			
INVESTIGATIONS			
subjects affected / exposed	118 / 336 (35.12%)	124 / 331 (37.46%)	
occurrences (all)	1365	1176	
Injury, poisoning and procedural complications			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
subjects affected / exposed	67 / 336 (19.94%)	26 / 331 (7.85%)	
occurrences (all)	69	29	
Cardiac disorders			
CARDIAC DISORDERS			

subjects affected / exposed	7 / 336 (2.08%)	8 / 331 (2.42%)	
occurrences (all)	7	11	
Nervous system disorders			
NERVOUS SYSTEM DISORDERS			
subjects affected / exposed	21 / 336 (6.25%)	34 / 331 (10.27%)	
occurrences (all)	25	48	
Blood and lymphatic system disorders			
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
subjects affected / exposed	303 / 336 (90.18%)	291 / 331 (87.92%)	
occurrences (all)	2746	2445	
Ear and labyrinth disorders			
EAR AND LABYRINTH DISORDERS			
subjects affected / exposed	1 / 336 (0.30%)	2 / 331 (0.60%)	
occurrences (all)	1	3	
Eye disorders			
EYE DISORDERS			
subjects affected / exposed	2 / 336 (0.60%)	1 / 331 (0.30%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
GASTROINTESTINAL DISORDERS			
subjects affected / exposed	54 / 336 (16.07%)	48 / 331 (14.50%)	
occurrences (all)	100	90	
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS			
subjects affected / exposed	6 / 336 (1.79%)	5 / 331 (1.51%)	
occurrences (all)	7	5	
Skin and subcutaneous tissue disorders			
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
subjects affected / exposed	13 / 336 (3.87%)	8 / 331 (2.42%)	
occurrences (all)	13	11	
Renal and urinary disorders			
RENAL AND URINARY DISORDERS			
subjects affected / exposed	13 / 336 (3.87%)	9 / 331 (2.72%)	
occurrences (all)	15	9	
Endocrine disorders			
ENDOCRINE DISORDERS			

subjects affected / exposed	1 / 336 (0.30%)	0 / 331 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
subjects affected / exposed	8 / 336 (2.38%)	7 / 331 (2.11%)	
occurrences (all)	17	11	
Infections and infestations			
INFECTIONS AND INFESTATIONS			
subjects affected / exposed	122 / 336 (36.31%)	118 / 331 (35.65%)	
occurrences (all)	196	194	
Metabolism and nutrition disorders			
METABOLISM AND NUTRITION DISORDERS			
subjects affected / exposed	30 / 336 (8.93%)	30 / 331 (9.06%)	
occurrences (all)	96	78	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2012	Request for modifications from the ANSM of the initial protocol before the start of the study (the main modification was to precise the principal objective paragraph).
10 August 2012	• "GELARC" replaced by "LYSARC"; "GELA" replaced by "LYSA" reflecting change to names of these organizations; • Suppression of certain evaluations and extension of the deadline for carrying out certain evaluations: vital signs before day 1 of each cycle and each evaluation, and complete blood cells count at Day 7 and 10 of each cycle • Addition of a new rule for SAE reporting: SAE linked to scheduled hospitalizations before patient randomization into the study should not be reported • Addition of a jugal epithelial cells sample for genomic study
30 October 2012	• This amendment follows the letter from the ANSM dated October 17, 2012, concerning a case of progressive multifocal leukoencephalopathy (PML) reported in a patient who was treated with GA101 (GA101). • Patients with a history of PML will not be included in the study. The exclusion criterion "Prior history of Progressive Multifocal Leukoencephalopathy (PML)" is added. • A neurological examination must be carried out during each clinical examination, during the treatment phase as well as during the follow-up phase, in order to detect any neurological signs suggestive of potential PML. • Information on what to do in case of suspected PML: symptoms, diagnosis, what to do with the administration of anti CD20. In the event of symptoms suggestive of PML, investigations must be carried out: consultation with a neurologist, brain MRI, search for the JC virus in the cerebrospinal fluid, etc. Treatment with Rituximab or GA101 should be suspended during investigations, and definitively stopped if the diagnosis of PML is confirmed.
12 December 2012	Change of tubes used for biological studies. Analysis of samples collected for the first patients included revealed that the stability of blood cells in EDTA tubes was not compatible with the achievement of standardized NFP. It was decided to keep the number of tubes taken per patient, i.e. 4 tubes, but to distribute these tubes as follows: - 2 EDTA tubes for genetic study - 2 heparin tubes for standardized NFP.

17 June 2013	Following the shortage of vindesine, possibility of replacing vindesine by vincristine for patients treated with ACVBP chemotherapy. In this study, the centers use CHOP or ACVBP as chemotherapy, according to their habits. This choice is valid for all patients in the same center and cannot be modified, the randomization being stratified on the choice of chemotherapy. Vindesine, a component of ACVBP, was out of stock worldwide (laboratory release dated June 7, 2013). This substitution should only take place in the event of a complete shortage of the stock of vindesine (dosage: D1 and D5 vincristine 0.7 mg / m2 without exceeding 1 mg total dose by injection, which makes a total dose of 1.4mg / m2 per cycle of ACVBP without exceeding 2 mg total dose).
28 July 2014	• Recommendations have been put in place to alert investigators on the increased toxicity of GA101 and the potential risks of severe infection: contraception until 18 months after last dose of GA101 instead of 12 months, changes in management of hematological toxicities, GA101 dose adjustments. • Addition and modification of blood and bone marrow samples for further biological analyzes.
10 February 2015	Following the announcement by the ANSM, on November 24, 2014, of the global shortage of BCNU (Carmustine), a drug forming part of the BEAM multidrug therapy (Carmustine, Etoposide, Cytarabine, Melphalan), proposal for 2 alternative conditioning regimes: - Benda-EAM polychemotherapy (Bendamustine, Etoposide, Cytarabine, Melphalan) - BAM polychemotherapy (Busulfan, Cytarabine, Melphalan
24 November 2015	Modification of the schedule of intermediate and final analyzes. Intermediate analysis n°3 after treatment phase of all patients and final analysis performed after the onset of 345 events

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/33211799