Clinical trial results:
Phase III Randomized, Open Label Study of Single Agent Ofatumumab vs. Single Agent Rituximab in Indolent B-Cell Non Hodgkin Lymphoma Relapsed After Rituximab Containing Therapy

Summary

EudraCT number	2010-018780-42
Trial protocol	SK CZ BG BE FR HU
Global end of trial date	19 December 2016

Results information

Result version number	v1 (current)
This version publication date	22 December 2017
First version publication date	22 December 2017

Trial information

Trial identification

Sponsor protocol code	COMB157D2303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01200589
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	19 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare PFS following therapy with single agent ofatumumab vs. single agent rituximab in subjects with iNHL that had relapsed after prior rituximab containing therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 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: 26
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	China: 36
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Japan: 116
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	United States: 84
Worldwide total number of subjects	438
EEA total number of subjects	117

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)	277
From 65 to 84 years	156
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to Ofatumumab or Rituximab.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ofatumumab

Arm description:

Four weekly doses of single agent ofatumumab 1000 mg by intravenous (i.v.) infusion, followed by ofatumumab 1000 mg i.v. every two months for four additional doses.

Arm type	Experimental
Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	OMB157
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Four weekly doses of single agent ofatumumab 1000 mg by intravenous (i.v.) infusion), followed by ofatumumab 1000 mg i.v. every two months for four additional doses.

Arm title	Rituximab

Arm description:

Four weekly doses of single agent rituximab 375 mg/m2 i.v., followed by rituximab 375 mg/m2 i.v. every two months for four additional doses.

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Four weekly doses of single agent rituximab 375 mg/m2 i.v., followed by rituximab 375 mg/m2 i.v. every two months for four additional doses.

Number of subjects in period 1	Ofatumumab	Rituximab
Started	219	219
Intent-to-treat (ITT) analysis set	219	219
Safety set	217	218
Completed	29	30
Not completed	190	189
Study terminated	170	172
Consent withdrawn by subject	13	11
Physician decision	2	2
Lost to follow-up	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Ofatumumab
Reporting group description:	
Four weekly doses of single agent ofatumumab 1000 mg by intravenous (i.v.) infusion, followed by ofatumumab 1000 mg i.v. every two months for four additional doses.	
Reporting group title	Rituximab
Reporting group description:	
Four weekly doses of single agent rituximab 375 mg/m2 i.v., followed by rituximab 375 mg/m2 i.v. every two months for four additional doses.	

Reporting group values	Ofatumumab	Rituximab	Total
Number of subjects	219	219	438
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	142	135	277
From 65-84 years	73	83	156
85 years and over	4	1	5
Age Continuous Units: Years			
arithmetic mean	60.8	60.7	
standard deviation	± 11.27	± 11.84	-
Gender, Male/Female Units: Subjects			
Female	115	109	224
Male	104	110	214

End points

End points reporting groups

Reporting group title	Ofatumumab
Reporting group description:	
Four weekly doses of single agent ofatumumab 1000 mg by intravenous (i.v.) infusion, followed by ofatumumab 1000 mg i.v. every two months for four additional doses.	
Reporting group title	Rituximab
Reporting group description:	
Four weekly doses of single agent rituximab 375 mg/m2 i.v., followed by rituximab 375 mg/m2 i.v. every two months for four additional doses.	

Primary: Progression-free survival (PFS) - Number of participants with PFS events

End point title	Progression-free survival (PFS) - Number of participants with PFS events
End point description:	
PFS was defined as the interval of time between the date of randomization and the earlier of the date of disease progression or death due to any cause. Disease response was assessed according to modified 2007 Revised Response Criteria for Malignant Lymphoma (RRCML). Computed tomography (CT) scans of the neck, thorax, abdomen and pelvis were performed as part of the efficacy evaluation. Bone marrow examination to confirm a suspected complete response (CR) was performed within 8 weeks following the onset of a CT scan confirmed CR. The number of patients with PFS events was assessed.	
End point type	Primary
End point timeframe:	
200 weeks	

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	219		
Units: Participants	114	117		

Statistical analyses

Statistical analysis title	Progression Free Survival
Comparison groups	Ofatumumab v Rituximab
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.49

Secondary: Number of participants with complete response (CR)

End point title	Number of participants with complete response (CR)

End point description:

Disease response was assessed according to modified 2007 Revised Response Criteria for Malignant Lymphoma (RRCML). Computed tomography (CT) scans of the neck, thorax, abdomen and pelvis were performed as part of the efficacy evaluation. Bone marrow examination to confirm a suspected complete response (CR) was performed within 8 weeks following the onset of a CT scan confirmed CR.

End point type	Secondary

End point timeframe:

200 weeks

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	219		
Units: Participants	36	44		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with overall response (OR)

End point title	Number of participants with overall response (OR)

End point description:

The overall response rate (ORR) was defined as the number of participants achieving a CR or partial response (PR). from start of randomization until disease progression, or the start of a new anti-cancer therapy. Disease response was assessed according to modified 2007 Revised Response Criteria for Malignant Lymphoma (RRCML). Computed tomography (CT) scans of the neck, thorax, abdomen and pelvis were performed as part of the efficacy evaluation. Bone marrow examination to confirm a suspected complete response (CR) was performed within 8 weeks following the onset of a CT scan confirmed CR.

End point type	Secondary

End point timeframe:

200 weeks

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	219		
Units: Participants	110	144		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) - Number of deaths

End point title	Overall survival (OS) - Number of deaths

End point description:

OS was defined as the interval of time between the date of randomization and the date of death due to any cause. The number of deaths were assessed.

End point type	Secondary

End point timeframe:

200 weeks

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	219		
Units: Participants	28	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with infection related adverse events

End point title	Number of participants with infection related adverse events

End point description:

The number of participants with infection related adverse events was assessed.

End point type	Secondary

End point timeframe:

200 weeks

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	218		
Units: Participants	69	81		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with infusion related adverse events due to study drug

End point title	Number of participants with infusion related adverse events due to study drug

End point description:

The number of participants with infusion related adverse events due to study drug was assessed.

End point type	Secondary

End point timeframe:

36 weeks + 60 days

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	218		
Units: Participants	178	112		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with myelosuppression adverse events

End point title	Number of participants with myelosuppression adverse events

End point description:

The number of participants with myelosuppression adverse events was assessed.

End point type	Secondary

End point timeframe:

200 weeks

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	218		
Units: Participants	24	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

End point type	Secondary

End point timeframe:
200 weeks

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: weeks				
number (not applicable)				

Notes:
[1] - The analysis of this end point was not performed due to the early termination of the study.
[2] - The analysis of this end point was not performed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next treatment

End point title	Time to next treatment

End point description:

End point type	Secondary

End point timeframe:
200 weeks

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: weeks				
number (not applicable)				

Notes:
[3] - The analysis of this end point was not performed due to the early termination of the study.
[4] - The analysis of this end point was not performed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics

End point title	Pharmacokinetics

End point description:

End point type	Secondary

End point timeframe:
70 weeks

End point values	Ofatumumab	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: mL				
number (not applicable)				

Notes:

[5] - The analysis of this end point was not performed due to the early termination of the study.

[6] - The analysis of this end point was not performed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Ofatumumab
Reporting group description:	
Ofatumumab	
Reporting group title	Rituximab
Reporting group description:	
Rituximab	

Serious adverse events	Ofatumumab	Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 217 (17.51%)	37 / 218 (16.97%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of appendix			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour pulmonary			

subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycosis fungoides			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			

subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 217 (0.92%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor peripheral circulation			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (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			

Asthenia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 217 (0.00%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asthma			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 217 (0.00%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 217 (0.00%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 217 (0.46%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 217 (0.00%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	5 / 217 (2.30%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 217 (0.46%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			

subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 217 (0.92%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Otosclerosis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ileus			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 217 (0.00%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 217 (0.46%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 217 (0.46%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph gland infection			

subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 217 (0.92%)	5 / 218 (2.29%)	
occurrences causally related to treatment / all	1 / 2	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 217 (0.46%)	3 / 218 (1.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 217 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ofatumumab	Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	177 / 217 (81.57%)	150 / 218 (68.81%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 217 (1.38%)	11 / 218 (5.05%)	
occurrences (all)	3	11	
Neutrophil count decreased			
subjects affected / exposed	10 / 217 (4.61%)	16 / 218 (7.34%)	
occurrences (all)	17	18	
White blood cell count decreased			
subjects affected / exposed	12 / 217 (5.53%)	23 / 218 (10.55%)	
occurrences (all)	19	29	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	40 / 217 (18.43%)	19 / 218 (8.72%)	
occurrences (all)	54	27	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 217 (5.07%)	20 / 218 (9.17%)	
occurrences (all)	13	35	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	6 / 217 (2.76%)	16 / 218 (7.34%)	
occurrences (all)	7	17	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	9 / 217 (4.15%)	14 / 218 (6.42%)	
occurrences (all)	11	14	
Chills			
subjects affected / exposed	8 / 217 (3.69%)	13 / 218 (5.96%)	
occurrences (all)	10	13	
Fatigue			
subjects affected / exposed	21 / 217 (9.68%)	28 / 218 (12.84%)	
occurrences (all)	23	30	
Pyrexia			
subjects affected / exposed	9 / 217 (4.15%)	21 / 218 (9.63%)	
occurrences (all)	10	25	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 217 (5.53%)	7 / 218 (3.21%)	
occurrences (all)	14	8	
Constipation			
subjects affected / exposed	17 / 217 (7.83%)	11 / 218 (5.05%)	
occurrences (all)	20	11	
Diarrhoea			
subjects affected / exposed	20 / 217 (9.22%)	15 / 218 (6.88%)	
occurrences (all)	25	17	
Nausea			
subjects affected / exposed	19 / 217 (8.76%)	16 / 218 (7.34%)	
occurrences (all)	21	19	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 217 (4.15%)	18 / 218 (8.26%)	
occurrences (all)	10	23	
Dyspnoea			
subjects affected / exposed	13 / 217 (5.99%)	13 / 218 (5.96%)	
occurrences (all)	14	13	
Oropharyngeal discomfort			
subjects affected / exposed	6 / 217 (2.76%)	11 / 218 (5.05%)	
occurrences (all)	17	13	

Oropharyngeal pain			
subjects affected / exposed	12 / 217 (5.53%)	11 / 218 (5.05%)	
occurrences (all)	14	14	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	20 / 217 (9.22%)	14 / 218 (6.42%)	
occurrences (all)	21	17	
Rash			
subjects affected / exposed	42 / 217 (19.35%)	11 / 218 (5.05%)	
occurrences (all)	51	13	
Rash maculo-papular			
subjects affected / exposed	16 / 217 (7.37%)	2 / 218 (0.92%)	
occurrences (all)	20	2	
Urticaria			
subjects affected / exposed	41 / 217 (18.89%)	3 / 218 (1.38%)	
occurrences (all)	42	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 217 (6.45%)	7 / 218 (3.21%)	
occurrences (all)	16	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 217 (3.69%)	11 / 218 (5.05%)	
occurrences (all)	8	15	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 217 (6.45%)	22 / 218 (10.09%)	
occurrences (all)	25	28	
Upper respiratory tract infection			
subjects affected / exposed	13 / 217 (5.99%)	11 / 218 (5.05%)	
occurrences (all)	15	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2010	• Revision of response criteria. • Sample size increased. • Several exclusion criteria amended to allow greater medical judgment in determining eligibility. • Premedication and infusion schedule information moved from SPM to protocol.
24 November 2010	• Addition of study logo and acronym. • Additional details added for the randomization method. • Inclusion and exclusion criteria modified to further define the subject population. • Acetaminophen pre-infusion medication requirement clarified. • Further define the OS analysis plan. • Addition of a Japanese specific HBV DNA monitoring schedule. Removal of a sample size re-estimation.
09 April 2013	• Further define the requirements for baseline bone marrow and lymphoma samples. • Inclusion and exclusion criteria modified to further define and clarify the subject population. • Clarification on study medication dosing and dose delays, including rapid infusion schedule use. • Clarifications to the ofatumumab pre-medication requirements. • Clarification concerning the management of ofatumumab related infusion reactions. • Response assessment updated to align more specifically with the Cheson 2007 criteria. • Clarifications to the pharmacokinetic sub-study sample collection requirements.
02 December 2013	• Exclusion criteria and guidelines for events of special interest were modified to clearly define the care and management of subjects with Hepatitis B. • Clarification visit scheduling requirements for HAHA/PK collection. • Revisions to the Time and Events Table to ensure consistency throughout the protocol. • Addition of Universal Trial Number (UTN): U1111-1148-8535 • Specified local laboratory information that must be entered into eCRF
05 August 2014	• Protocol title was replaced with FL with iNHL. • In addition to FL grades 1-3A, other types of iNHL were included in eligibility criteria. • In addition to stratification by FLIPI-1 score (0-2 vs. 3-5, for FL subjects only) and last prior rituximab therapy (monotherapy vs. combination therapy), subjects were to be stratified by disease type (FL vs. Non-FL). • Since this study used an IDMC and not an Independent Safety Review Committee (iSRC), only the IDMC is referenced.
16 July 2016	• Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship. • Make administrative changes to align with Novartis processes and procedures. • The previous protocol Id was OMB113676, which is now owned by Novartis. The Novartis code is OMB157D2303. Both codes are being used for this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated due to futility of the primary end point.

Notes: