



Clinical trial results:

An Open-label, Multicentre, Nonrandomized, Dose-escalating Phase I/II Study, With a Randomized Phase II Part, to Investigate the Safety and Tolerability of RO5072759 Given as Monotherapy in Patients With CD20+ Malignant Disease.

Summary

EudraCT number	2007-001103-37
Trial protocol	DE
Global end of trial date	25 November 2013

Results information

Result version number	v2 (current)
This version publication date	12 June 2016
First version publication date	12 August 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO20999
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00517530
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

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 May 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for the phase I part of the study is to investigate the safety and tolerability of escalating intravenous (IV) doses of obinutuzumab given as monotherapy in patients with CD20+ (tumour infiltrating lymphocytic) Malignant Disease, including B-cell chronic lymphocytic leukemia (CLL) and NonHodgkin's Lymphoma (NHL). The primary objective for the phase II part of the study is to investigate the efficacy and safety of one dose of obinutuzumab in patients with relapsed/refractory CLL and NHL that is, in turn, either indolent (iNHL) or aggressive (aNHL).

This is an open label dose escalating study in phase I and open label in phase II, but the two doses in iNHL & aNHL are randomised (to high or low dose of the same open label treatment). CLL was not randomised as only one dose level was used.

Patients with a response who might gain additional benefit from being treated again in the opinion of the investigator may be enrolled in a Retreatment Period.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 131
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	134
EEA total number of subjects	134

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)	70
From 65 to 84 years	64
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Different patients were recruited into Phase I and Phase II. Some of those same patients were included in follow-up, even if they did not complete treatment.

Pre-assignment

Screening details:

Phase I of this study recruited patients with CD20+ (tumour infiltrating lymphocytic) Malignant Disease, including B-cell chronic lymphocytic leukemia (CLL) and NonHodgkin's Lymphoma (NHL). Phase II recruited patients with relapsed/refractory CLL and indolent (iNHL) or aggressive (aNHL).

Period 1

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

Blinding implementation details:

This is an open label dose escalating study in phase I and open label in phase II, but the two doses in iNHL & aNHL are randomised (to high or low dose of the same open label treatment). CLL was not randomised as only one dose level was used.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I, CLL

Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	Phase I, NHL
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Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	400/400 mg - Phase II, iNHL
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Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	1600/800 mg - Phase II, iNHL
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Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	400/400 mg - Phase II, aNHL
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Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	1600/800 mg - Phase II, aNHL
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Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	1000/1000 mg - Phase II, CLL
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Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
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Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Number of subjects in period 1	Phase I, CLL	Phase I, NHL	400/400 mg - Phase II, iNHL
Started	13	21	18
Completed	13	11	13
Not completed	0	10	5
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	-	-
Administrative reasons	-	2	-
Lack of efficacy	-	7	5
Protocol deviation	-	-	-

Number of subjects in period 1	1600/800 mg - Phase II, iNHL	400/400 mg - Phase II, aNHL	1600/800 mg - Phase II, aNHL
Started	22	21	19
Completed	18	9	9
Not completed	4	12	10
Adverse event, serious fatal	1	2	-
Consent withdrawn by subject	-	-	-
Administrative reasons	-	-	-
Lack of efficacy	3	10	10
Protocol deviation	-	-	-

Number of subjects in period 1	1000/1000 mg - Phase II, CLL
Started	20
Completed	13
Not completed	7
Adverse event, serious fatal	3
Consent withdrawn by subject	1
Administrative reasons	-
Lack of efficacy	2
Protocol deviation	1

Period 2

Period 2 title	Follow up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is an open-label dose-escalating study in phase I and open-label in phase II, but the iNHL & aNHL patients are randomised (to high or low dose of the same open label treatment). CLL was not randomised as only one dose level was used.

Arms

Are arms mutually exclusive?	No
Arm title	Phase I, NHL

Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	Phase I, CLL
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Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	400/400 mg - Phase II, iNHL
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Arm description:

Obinutuzumab intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.

Arm title	1600/800 mg - Phase II, iNHL
Arm description: Obinutuzumab intravenous infusion	
Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.	
Arm title	400/400 mg - Phase II, aNHL
Arm description: Obinutuzumab intravenous infusion	
Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.	
Arm title	1600/800 mg - Phase II, aNHL
Arm description: Obinutuzumab intravenous infusion	
Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.	
Arm title	1000/1000 mg - Phase II, CLL
Arm description: Obinutuzumab intravenous infusion	
Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	RO5072759
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Obinutuzumab was provided in single-dose glass vials as a freeze-dried powder for solution for intravenous administration.	

Number of subjects in period 2	Phase I, NHL	Phase I, CLL	400/400 mg - Phase II, iNHL
Started	20	13	17
Completed	2	0	0
Not completed	18	13	17
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	1	-
Administrative reasons	2	1	3
Lost to follow-up	-	-	1
Lack of efficacy	15	11	12
Did not cooperate	-	-	-

Number of subjects in period 2	1600/800 mg - Phase II, iNHL	400/400 mg - Phase II, aNHL	1600/800 mg - Phase II, aNHL
Started	21	17	16
Completed	1	1	0
Not completed	20	16	16
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	1
Administrative reasons	7	2	3
Lost to follow-up	-	-	-
Lack of efficacy	13	14	12
Did not cooperate	-	-	-

Number of subjects in period 2	1000/1000 mg - Phase II, CLL
Started	19
Completed	1
Not completed	18
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Administrative reasons	3
Lost to follow-up	-
Lack of efficacy	11
Did not cooperate	1

Baseline characteristics

Reporting groups	
Reporting group title	Phase I, CLL
Reporting group description: Obinutuzumab intravenous infusion	
Reporting group title	Phase I, NHL
Reporting group description: Obinutuzumab intravenous infusion	
Reporting group title	400/400 mg - Phase II, iNHL
Reporting group description: Obinutuzumab intravenous infusion	
Reporting group title	1600/800 mg - Phase II, iNHL
Reporting group description: Obinutuzumab intravenous infusion	
Reporting group title	400/400 mg - Phase II, aNHL
Reporting group description: Obinutuzumab intravenous infusion	
Reporting group title	1600/800 mg - Phase II, aNHL
Reporting group description: Obinutuzumab intravenous infusion	
Reporting group title	1000/1000 mg - Phase II, CLL
Reporting group description: Obinutuzumab intravenous infusion	

Reporting group values	Phase I, CLL	Phase I, NHL	400/400 mg - Phase II, iNHL
Number of subjects	13	21	18
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	7	11	14
>=65 years	6	10	4
Age continuous Units: years			
median	64	64	61.5
full range (min-max)	39 to 83	46 to 81	44 to 76
Gender, Male/Female Units: participants			
Female	4	12	6
Male	9	9	12

Reporting group values	1600/800 mg - Phase II, iNHL	400/400 mg - Phase II, aNHL	1600/800 mg - Phase II, aNHL
Number of subjects	22	21	19
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	14	6	7
>=65 years	8	15	12

Age continuous Units: years median full range (min-max)	51 42 to 79	70 43 to 80	72 22 to 85
Gender, Male/Female Units: participants			
Female	9	8	5
Male	13	13	14

Reporting group values	1000/1000 mg - Phase II, CLL	Total	
Number of subjects	20	134	
Age Categorical Units: participants			
<=18 years	0	0	
Between 18 and 65 years	11	70	
>=65 years	9	64	
Age continuous Units: years median full range (min-max)	62.5 36 to 81	-	
Gender, Male/Female Units: participants			
Female	8	52	
Male	12	82	

End points

End points reporting groups

Reporting group title	Phase I, CLL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	Phase I, NHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	400/400 mg - Phase II, iNHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	1600/800 mg - Phase II, iNHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	400/400 mg - Phase II, aNHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	1600/800 mg - Phase II, aNHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	1000/1000 mg - Phase II, CLL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	Phase I, NHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	Phase I, CLL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	400/400 mg - Phase II, iNHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	1600/800 mg - Phase II, iNHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	400/400 mg - Phase II, aNHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	1600/800 mg - Phase II, aNHL
Reporting group description:	
Obinutuzumab intravenous infusion	
Reporting group title	1000/1000 mg - Phase II, CLL
Reporting group description:	
Obinutuzumab intravenous infusion	
Subject analysis set title	PD 400/400 mg - Phase II, iNHL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacodynamics: 400/400 mg - Phase II, iNHL patients with peripheral B-cell depletion at end of treatment.	
Subject analysis set title	PD 1600/800 mg - Phase II, iNHL

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacodynamics 1600/800 mg - Phase II, iNHL patients with B-cell depletion at end of treatment.	
Subject analysis set title	PD 400/400 mg - Phase II, aNHL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacodynamics 400/400 mg - Phase II, aNHL with B-cell depletion at end of treatment.	
Subject analysis set title	PD 1600/800 mg - Phase II, aNHL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacodynamics 1600/800 mg - Phase II, aNHL with B-cell depletion at end of treatment.	
Subject analysis set title	PD 1000/1000 mg - Phase II, CLL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacodynamics 1000/1000 mg - Phase II, CLL patients with B-cell depletion at end of treatment.	
Subject analysis set title	Retreated Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who might benefit from retreatment who were allowed to be treated again via intravenous infusion of obinutuzumab at the request of the investigator.	
Subject analysis set title	PK 400 mg - Phase I, NHL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics PK 400 mg - Phase I, NHL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for $n \geq 3$.	
Subject analysis set title	PK 800 mg - Phase I, NHL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics PK 800 mg - Phase I, NHL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for $n \geq 3$. Also, one subject in this group was inadvertently given an incorrect dose on Day 1, but continued throughout the rest of the trial at the 400 mg dose.	
Subject analysis set title	PK 1200 mg - Phase I, NHL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics (PK) 1200 mg - Phase I, NHL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for $n \geq 3$.	
Subject analysis set title	PK 2000 mg - Phase I, NHL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics (PK) 2000 mg - Phase I, NHL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for $n \geq 3$.	
Subject analysis set title	PK 800 mg - Phase I, CLL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics PK 800 mg - Phase I, CLL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for $n \geq 3$.	
Subject analysis set title	PK 1000 mg - Phase I, CLL

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics PK 1000 mg - Phase I, CLL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for n ≥ 3.	
Subject analysis set title	PK 1200 mg - Phase I, CLL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics PK 1200 mg - Phase I, CLL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for n ≥ 3.	
Subject analysis set title	PK 2000 mg - Phase I, CLL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics PK 2000 mg - Phase I, CLL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for n ≥ 3.	
Subject analysis set title	PK 100 mg - Phase I, NHL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetics PK 100 mg - Phase I, CLL Safety population - All enrolled participants in Phase I, who had received at least 1 dose of obinutuzumab, but some participants were excluded from the analysis due to limited PK sampling or due to wrong tube selection at site. Data only reported for groups with data for n ≥ 3.	
Subject analysis set title	Phase II - iNHL
Subject analysis set type	Full analysis
Subject analysis set description:	
All iNHL patients in Phase II	
Subject analysis set title	Phase II - aNHL
Subject analysis set type	Full analysis
Subject analysis set description:	
All aNHL patients in Phase II	
Subject analysis set title	Phase II - CLL
Subject analysis set type	Full analysis
Subject analysis set description:	
All CLL patients in Phase II	

Primary: Percentage of participants who experienced a dose-limiting toxicity in Phase I of the study

End point title	Percentage of participants who experienced a dose-limiting toxicity in Phase I of the study ^[1]
End point description:	
Dose-limiting toxicities were defined as obinutuzumab-related adverse events occurring within the first 28 days of each administration of obinutuzumab, with the exception of B-cell depletion and lymphopenia which are expected outcomes of treatment with obinutuzumab.	
End point type	Primary
End point timeframe:	
Baseline to 28 days after the last infusion of obinutuzumab (up to 6 months)	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All baseline arms were not included in the analysis- only Phase I arms were included in this analysis.

End point values	Phase I, CLL	Phase I, NHL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	21		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

Statistical analysis title	Analysis Not Possible
Statistical analysis description: Statistical analysis was not possible, as no subjects reached dose limiting toxicity.	
Comparison groups	Phase I, NHL v Phase I, CLL
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 9999
Method	No analysis was possible

Notes:

[2] - No analysis was possible.

Primary: Percentage of participants with Best Overall Response

End point title	Percentage of participants with Best Overall Response ^[3]
End point description: Best overall response (BOR) was defined as the percentage of participants with a complete response (CR) or partial response (PR)	
End point type	Primary
End point timeframe: by Cutoff Date: 31MAR2012	

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All baseline arms were not included in the analysis- only Phase II arms were included in this analysis.

End point values	400/400 mg - Phase II, iNHL	1600/800 mg - Phase II, iNHL	400/400 mg - Phase II, aNHL	1600/800 mg - Phase II, aNHL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	22	21	19
Units: percentage of participants				
number (not applicable)	33.3	63.6	23.8	36.8

End point values	1000/1000 mg - Phase II, CLL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of participants				
number (not applicable)	30			

Statistical analyses

Statistical analysis title	Difference in Response Rates iNHL
Comparison groups	400/400 mg - Phase II, iNHL v 1600/800 mg - Phase II, iNHL
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	30.3
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	7.6
upper limit	53

Secondary: Percentage of Participants with Complete Response (CR/CRu/CRi)

End point title	Percentage of Participants with Complete Response (CR/CRu/CRi) ^[4]
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End point description:

A complete response was defined as the disappearance of all evidence of disease (NHL) and symptoms; normalization of biochemical abnormalities (NHL); regression of lymph nodes and nodal masses to normal size; decrease of nodes in the sum of the products of the greatest diameters (SPD); regression in size of the spleen and/or liver, should not be palpable, and disappearance of nodules related to lymphoma (CLL). Complete/unconfirmed (CRu) response includes NHL patients with one or more of the following: 1) a residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD; 2) Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia). Complete Response with Incomplete Bone Marrow Recovery (CRi) was measured only in patients with CLL. Data not measured in a specific arm are identified with "9999".

End point type	Secondary
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End point timeframe:

by Cutoff Date: 31MAR2012

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All baseline arms were not included in the analysis- only Phase II arms were included in this analysis.

End point values	400/400 mg - Phase II, iNHL	1600/800 mg - Phase II, iNHL	400/400 mg - Phase II, aNHL	1600/800 mg - Phase II, aNHL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	22	21	19
Units: percentage of participants				
number (not applicable)				
CR	5.6	13.6	9.5	15.8
CRu	5.6	9.1	4.8	0
CRi	9999	9999	9999	9999

End point values	1000/1000 mg - Phase II, CLL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of participants				
number (not applicable)				
CR	5			
CRu	9999			
CRI	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Partial Response (PR)

End point title	Percentage of Participants with Partial Response (PR) ^[5]
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End point description:

A PR was defined as a $\geq 50\%$ decrease in SPD of the 6 largest nodes or nodal masses; no increase in size of other nodes, liver, or spleen; regression of splenic and hepatic nodules by $\geq 50\%$ in their SPD or, for single nodules, in the long axis (CLL only); and no new disease sites.

End point type	Secondary
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End point timeframe:

by Cutoff Date: 31MAR2012

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All baseline arms were not included in the analysis- only Phase II arms were included in this analysis.

End point values	400/400 mg - Phase II, iNHL	1600/800 mg - Phase II, iNHL	400/400 mg - Phase II, aNHL	1600/800 mg - Phase II, aNHL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	22	21	19
Units: participants				
number (not applicable)	22.2	40.9	9.5	21.1

End point values	1000/1000 mg - Phase II, CLL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants				
number (not applicable)	25			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) in Phase II of the study

End point title	Progression-free survival (PFS) in Phase II of the study ^[6]
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End point description:

PFS was defined as the time from start of treatment to disease progression (PD) or death due to any cause, whichever occurred first. For non-Hodgkin's lymphoma participants, PD was defined as $\geq 50\%$ increase from nadir in the sum of the products of the greatest diameters (SPD) of any previously identified abnormal node for participants with a partial response or non-responders or the appearance of any new lesion during or at the end of therapy. For chronic lymphocytic leukemia participants, PD was defined as: (1) A $\geq 50\%$ increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules); a lymph node with a short axis of < 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm or > 1.5 cm in the longest axis. (2) Appearance of any new lesion > 1 cm in the short axis. (4) A new site that is PET-positive with histological confirmation.

End point type	Secondary
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End point timeframe:

Beginning of treatment to the end of follow-up in Phase II of the study (up to 2 years, 3 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All baseline arms were not included in the analysis- only Phase II arms were included in this analysis.

End point values	400/400 mg - Phase II, iNHL	1600/800 mg - Phase II, iNHL	400/400 mg - Phase II, aNHL	1600/800 mg - Phase II, aNHL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	22	21	19
Units: days				
median (confidence interval 95%)	182 (106 to 526)	361 (343 to 678)	78 (42 to 260)	83 (43 to 339)

End point values	1000/1000 mg - Phase II, CLL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: days				
median (confidence interval 95%)	324 (217 to 357)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response in Phase II of the study

End point title	Duration of response in Phase II of the study
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End point description:

Duration of complete response was defined as the time from the first complete or partial response until disease progression (PD) or death, whichever occurred first. For non-Hodgkin's lymphoma participants, PD was defined as $\geq 50\%$ increase from nadir in the sum of the products of the greatest diameters

(SPD) of any previously identified abnormal node for participants with a partial response or non-responders or the appearance of any new lesion during or at the end of therapy. For chronic lymphocytic leukemia participants, PD was defined as: (1) A $\geq 50\%$ increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules); a lymph node with a short axis of < 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm or > 1.5 cm in the longest axis. (2) Appearance of any new lesion > 1 cm in the short axis. (4) A new site that is PET-positive with histological confirmation.

End point type	Secondary
End point timeframe:	
Beginning of treatment to the end of follow-up in Phase II of the study (up to 2 years, 3 months)	

End point values	Phase II - iNHL	Phase II - aNHL	Phase II - CLL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	12	6	
Units: days				
median (full range (min-max))	523 (23 to 952)	298 (95 to 929)	272.5 (23 to 794)	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Event-Free Survival (EFS)

End point title	Participants with Event-Free Survival (EFS) ^[7]
End point description:	
EFS is defined as the time from start of treatment to disease progression/relapse, death or, in case of early withdrawal from the treatment period, the (end) date of last dose, whatever comes first.	
End point type	Secondary
End point timeframe:	
by the end of the follow-up period	

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All baseline arms were not included in the analysis- only Phase II arms were included in this analysis.

End point values	400/400 mg - Phase II, iNHL	1600/800 mg - Phase II, iNHL	400/400 mg - Phase II, aNHL	1600/800 mg - Phase II, aNHL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	22	21	19
Units: participants				
number (not applicable)	5	6	2	3

End point values	1000/1000 mg - Phase II, CLL			
Subject group type	Reporting group			
Number of subjects analysed	20			

Units: participants				
number (not applicable)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) of obinutuzumab in NHL patients

End point title	Maximum plasma concentration (Cmax) of obinutuzumab in NHL patients
End point description: GA101 Serum PK Parameters in NHL Patients Following Ascending Doses of GA101.	
End point type	Secondary
End point timeframe: at Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 8	

End point values	PK 400 mg - Phase I, NHL	PK 800 mg - Phase I, NHL	PK 1200 mg - Phase I, NHL	PK 2000 mg - Phase I, NHL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	6	6	6
Units: micrograms/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=4,6,6,0)	134 (± 27.1)	234 (± 63.1)	307 (± 30.6)	0 (± 0)
Cycle 1 Day 8 (n=0,4,6,6)	0 (± 0)	367 (± 24.2)	449 (± 26.4)	714 (± 28.6)
Cycle 8 (n=0,5,5,5)	0 (± 0)	698 (± 65.4)	1070 (± 62.6)	1380 (± 66.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve of obinutuzumab administered on Day 1 of Cycle 1 in Phase I of the study

End point title	Area under the concentration-time curve of obinutuzumab administered on Day 1 of Cycle 1 in Phase I of the study
End point description: Blood samples were taken on Day 1 (pre-infusion, end of infusion, 3-6 hours post-infusion) of Cycle 1. Nonlinear mixed-effects modeling (with NONMEM software) was used to analyze the dose-concentration-time data of obinutuzumab.	
End point type	Secondary
End point timeframe: Day 1 of Cycle 1	

End point values	PK 400 mg - Phase I, NHL	PK 800 mg - Phase I, NHL	PK 1200 mg - Phase I, NHL	PK 100 mg - Phase I, NHL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	6	6	3
Units: microgram*day/mL				
geometric mean (geometric coefficient of variation)	459 (\pm 64.7)	993 (\pm 30.5)	1057 (\pm 60.5)	146 (\pm 49.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics: Participants with peripheral B-cell recovery after having had depletion at end of treatment

End point title	Pharmacodynamics: Participants with peripheral B-cell recovery after having had depletion at end of treatment
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End point description:

Participants analyzed include those with B-cell depletion at the end of treatment (N), with assessments (n) at each time point.

End point type	Secondary
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End point timeframe:

within and after 24 months of follow-up

End point values	PD 400/400 mg - Phase II, iNHL	PD 1600/800 mg - Phase II, iNHL	PD 400/400 mg - Phase II, aNHL	PD 1600/800 mg - Phase II, aNHL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16 ^[8]	21 ^[9]	21 ^[10]	19 ^[11]
Units: participants				
number (not applicable)				
within 6 months (n=11,19,11,12,13)	0	0	0	0
within 9 months (n=8,17,6,5,10)	0	0	0	1
within 12 months (n=5,16,4,5,9)	0	2	1	0
within 18 months (n=4,13,3,3,8)	0	1	0	1
within 24 months (n=3,10,2,3,5)	2	2	1	0
after 24 months (n=3,4,1,2,0)	1	0	0	1

Notes:

[8] - n= # patients with depletion at end of treatment

[9] - n= # patients with depletion at end of treatment

[10] - n= # patients with depletion at end of treatment

[11] - n= # patients with depletion at end of treatment

End point values	PD 1000/1000 mg - Phase II, CLL			
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Subject group type	Subject analysis set			
Number of subjects analysed	16 ^[12]			
Units: participants				
number (not applicable)				
within 6 months (n=11,19,11,12,13)	3			
within 9 months (n=8,17,6,5,10)	0			
within 12 months (n=5,16,4,5,9)	3			
within 18 months (n=4,13,3,3,8)	2			
within 24 months (n=3,10,2,3,5)	2			
after 24 months (n=3,4,1,2,0)	0			

Notes:

[12] - n= # patients with depletion at end of treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Retreated Participants with Response

End point title	Percentage of Retreated Participants with Response
End point description:	
Patients who might benefit from retreatment were allowed to be treated again at the request of the investigator.	
End point type	Secondary
End point timeframe:	
by Cutoff Date: 25NOV2013	

End point values	Retreated Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: percentage of participants				
number (not applicable)				
Best overall response	62			
Complete response	23			
Partial response	38			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum plasma concentration (Cmax) of obinutuzumab in CLL patients

End point title	Maximum plasma concentration (Cmax) of obinutuzumab in CLL patients
End point description:	
End point type	Other pre-specified

End point timeframe:

at Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 8

End point values	PK 800 mg - Phase I, CLL	PK 1000 mg - Phase I, CLL	PK 1200 mg - Phase I, CLL	PK 2000 mg - Phase I, CLL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	4	4	4
Units: micrograms/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=3,3,3,0)	216 (± 34.1)	210 (± 74)	307 (± 21.4)	0 (± 0)
Cycle 1 Day 8 (n=0,0,3,3)	0 (± 0)	0 (± 0)	437 (± 11.8)	735 (± 9.79)
Cycle 8 (n=3,3,3,4)	485 (± 48.1)	573 (± 73.2)	741 (± 32.8)	1730 (± 32.6)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through final cut off in November 2013

Adverse event reporting additional description:

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Safety Population
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Reporting group description:

Safety-Evaluable Participants

Note that the total number of deaths resulting from adverse events (AEs) reflects those from treatment-related AEs.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 134 (34.33%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cancer			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			

subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 134 (2.99%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Tooth avulsion			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Acute coronary syndrome			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiorespiratory arrest			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	5 / 134 (3.73%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		

Neutropenia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aplasia pure red cell			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer perforation			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pancreatitis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic abscess			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gingivitis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Haemophilus infection			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumococcal sepsis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumococcal infection			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Streptococcal infection			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			

subjects affected / exposed	4 / 134 (2.99%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 134 (91.79%)		
Investigations			
Weight decreased			
subjects affected / exposed	10 / 134 (7.46%)		
occurrences (all)	10		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	107 / 134 (79.85%)		
occurrences (all)	107		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	8		
Insomnia			
subjects affected / exposed	10 / 134 (7.46%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	19 / 134 (14.18%)		
occurrences (all)	19		
Thrombocytopenia			
subjects affected / exposed	15 / 134 (11.19%)		
occurrences (all)	15		
Neutropenia			
subjects affected / exposed	18 / 134 (13.43%)		
occurrences (all)	18		
Anaemia			

subjects affected / exposed occurrences (all)	18 / 134 (13.43%) 18		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	35 / 134 (26.12%)		
occurrences (all)	35		
Oedema peripheral			
subjects affected / exposed	12 / 134 (8.96%)		
occurrences (all)	12		
Fatigue			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	13 / 134 (9.70%)		
occurrences (all)	13		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 134 (8.21%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	23 / 134 (17.16%)		
occurrences (all)	23		
Nausea			
subjects affected / exposed	12 / 134 (8.96%)		
occurrences (all)	12		
Abdominal pain			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 134 (14.18%)		
occurrences (all)	19		
Dyspnoea			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	9		
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	8		
Muscle spasms			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	8		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 134 (11.19%)		
occurrences (all)	15		
Bronchitis			
subjects affected / exposed	15 / 134 (11.19%)		
occurrences (all)	15		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2007	Amendment A, dated before first subject first visit Protocol amendment A was issued before first subject first visit, so changes were incorporated into the initial final protocol before first subject first visit (on September 18, 2007).
01 April 2008	Amendment B, dated April 1, 2008 Protocol amendment B was issued before the start of patient enrollment in Phase II, to provide clarity around the patient population, that the text refers to the adult B-CLL population.
12 September 2008	Amendment C, dated September 12, 2008 Protocol amendment C was issued before the start of patient enrollment in Phase II, based on the per protocol interim analysis scheduled to occur after the last patient enrolled in cohort 4 completed the cycle 4 response assessments. The objective of the interim analysis was to identify a single dose to take forward into the phase II NHL patient population. Re-treatment was also introduced at this time, with details provided as applicable for this sub-population. Following a thorough review of all available clinical, laboratory and pharmacokinetic data the participating investigators agreed (on July 10, 2008) that it was not possible to choose a single dose of the study drug to take into phase II. No dose limiting toxicities had been observed at doses up to 2000 mg. Preliminary efficacy data also indicated activity across all dose levels administered to date. The reviewers advised that it would be valuable for the drug's development to open the phase II part of the study exploring two doses. The two doses selected for NHL patients in the phase II part of the study were: <ul style="list-style-type: none">• 1600mg iv infusion on Cycle 1, days 1 and 8, and 800mg iv infusion for on day 1 of Cycles 2 to 8• 400mg iv infusion on Cycle 1, days 1 and 8 and 400mg on day 1 of Cycles 2 to 8 The investigators also recommended that the two doses selected for the phase II part of the study should be tested in two relapsed/refractory CD20+ NHL populations: <ul style="list-style-type: none">• Indolent NHL (40 patients [20 patients 1600/800mg and 20 patients 400mg])• Aggressive NHL (40 patients [20 patients 1600/800mg and 20 pts 400mg])
09 April 2009	Amendment D, dated April 09, 2009 Protocol amendment D was issued after the start of patient enrollment in the study (April 09, 2009) and included a justification for the selected Phase II CLL dose. Updates were also made to the primary objective of this part of the study as well as the study design (addition of an extra infusion on Day 15 and agreement to proceed with a 1000 mg flat dose for Phase II CLL patients). This amendment also introduced opportunity for re-treatment if believed to be beneficial for a patient by investigator, and such a request was made.
20 December 2011	Amendment E, dated December 20, 2011 Protocol amendment E was issued on December 20, 2011. The main purpose of the amendment was to clarify the definition of end-of-study. The end-of-study was now defined as "2 years after the last patient has entered re-treatment unless all patients have left the study prior to this point," rather than "2 years after the last patient has been enrolled into the study, unless all patients have discontinued the study prior to this time- point." The schedule of assessments and other related text were adapted according to this clarification. Patients who were re-treated were considered to have withdrawn from follow-up. Follow-up data for re-treated patients was presented in a separate, but affiliated Clinical Study Report.

21 November 2012	<p>AMENDMENT F, dated November 21, 2012</p> <p>The protocol was further amended to address a request from France's Agence Nationale de Sécurité Medicament (ANSM) on 17 October 2012 to provide guidance on the diagnosis, evaluation, and management of a potential case of progressive multifocal leukoencephalopathy (PML). This protocol version was the subject of a country-specific amendment and implemented only in France.</p>
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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.

Pharmacodynamic results were limited because number of participants was inversely proportional to length of follow-up. In other words, there were fewer participants still in the trial as the follow-up period became longer.

Notes: