Clinical trial results:
A Phase III, Open Label, Randomized Trial of Ofatumumab Added to Fludarabine-Cyclophosphamide vs. Fludarabine-Cyclophosphamide Combination in Subjects with Relapsed Chronic Lymphocytic Leukemia

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2008-005811-16
Trial protocol	NL DE GR IT ES GB BG RO
Global end of trial date	25 October 2017

Results information

Result version number	v1 (current)
This version publication date	04 November 2018
First version publication date	04 November 2018

Trial information

Trial identification

Sponsor protocol code	110913

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00824265
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, Novartis.email@novartis.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	25 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare PFS of subjects treated with O+FC for the treatment of relapsed CLL to those treated with FC

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	12 March 2009
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	Brazil: 10
Country: Number of subjects enrolled	Bulgaria: 14
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	India: 29
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 90
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Ukraine: 66

Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	365
EEA total number of subjects	188

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)	231
From 65 to 84 years	133
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants (par) were screened within 14 days prior to the start of study drug administration to determine eligibility.

Pre-assignment

Screening details:

Eligible par were stratified by Stage (Binet A vs. B vs. C) and number of prior therapies (1-2 vs. ≥3). Par in each stratum were then centrally randomized in a 1:1 ratio to recive intravenous (IV) fludarabine and cyclophosphamide in combination with ofatumumab or IV fludarabine and cyclophosphamide alone.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects

Arm description:

Participants with relapsed CLL received IV infusions of ofatumumab in combination with fludarabine and cyclophosphamide IV infusions for 6 cycles; each cycle comprised of 28 days. Participants received ofatumumab administered at 300 milligram (mg) on Day 1, 1000 mg on Day 8 of cycle 1 and 1000 mg on Day 1 of cycles 2, 3, 4, 5 and 6. Fludarabine was administered at 25 mg/meter squared [m^2] and cyclophosphamide was administered at 250mg/m^2 on Days 1-3 of each cycles (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

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

Dosage and administration details:

Cycle 1-Day 1 300mg, Cycle 1-Day 8 1000mg, then Cycles 2-6 Day 1 1000mg every 28 days

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

Dosage and administration details:

Fludarabine 25mg/m^2 Days 1-3 every 28 days for 6 cycles

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

Dosage and administration details:

Cyclophosphamide 250 mg/m2 Days 1-3 every 28 days for 6 cycles

Arm title	Fludarabine + Cyclophosphamide_ ITT subjects

Arm description:

Participants with relapsed CLL received IV infusions of fludarabine administered at 25 mg/m^2 and cyclophosphamide administered at 250mg/m^2 on Days 1-3 of each cycle (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

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

Dosage and administration details:

Cyclophosphamide 250 mg/m2 Days 1-3 every 28 days for 6 cycles

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

Dosage and administration details:

Fludarabine 25mg/m^2 Days 1-3 every 28 days for 6 cycles

Number of subjects in period 1	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects
Started	183	182
Completed	119	102
Not completed	64	80
Physician decision	6	12
Consent withdrawn by subject	6	15
Adverse Event,non-fatal	50	52
Lost to follow-up	1	1
Protocol deviation	1	-

Period 2

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

Arms

Are arms mutually exclusive?	No

Arm title	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects

Arm description:

Participants with relapsed CLL received IV infusions of ofatumumab in combination with fludarabine and cyclophosphamide IV infusions for 6 cycles; each cycle comprised of 28 days. Participants received ofatumumab administered at 300 milligram (mg) on Day 1, 1000 mg on Day 8 of cycle 1 and 1000 mg on Day 1 of cycles 2, 3, 4, 5 and 6. Fludarabine was administered at 25 mg/meter squared [m^2] and cyclophosphamide was administered at 250mg/m^2 on Days 1-3 of each cycles (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

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

Dosage and administration details:

Cycle 1-Day 1 300mg, Cycle 1-Day 8 1000mg, then Cycles 2-6 Day 1 1000mg every 28 days

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

Dosage and administration details:

Cyclophosphamide 250 mg/m2 Days 1-3 every 28 days for 6 cycles

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

Dosage and administration details:

Fludarabine 25mg/m^2 Days 1-3 every 28 days for 6 cycles

Arm title	Fludarabine + Cyclophosphamide_ ITT subjects

Arm description:

Participants with relapsed CLL received IV infusions of fludarabine administered at 25 mg/m^2 and cyclophosphamide administered at 250mg/m^2 on Days 1-3 of each cycle (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

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

Dosage and administration details:

Fludarabine 25mg/m^2 Days 1-3 every 28 days for 6 cycles

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

Dosage and administration details:

Cyclophosphamide 250 mg/m2 Days 1-3 every 28 days for 6 cycles

Number of subjects in period 2	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects
Started	172	160
Completed	154	129
Not completed	18	31
w/drew consent, no f/u, or MD choice	18	31

Period 3

Period 3 title	Survival follow-up phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects

Arm description:

Participants with relapsed CLL received IV infusions of ofatumumab in combination with fludarabine and cyclophosphamide IV infusions for 6 cycles; each cycle comprised of 28 days. Participants received ofatumumab administered at 300 milligram (mg) on Day 1, 1000 mg on Day 8 of cycle 1 and 1000 mg on Day 1 of cycles 2, 3, 4, 5 and 6. Fludarabine was administered at 25 mg/meter squared [m^2] and cyclophosphamide was administered at 250mg/m^2 on Days 1-3 of each cycles (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

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

Dosage and administration details:

Cycle 1-Day 1 300mg, Cycle 1-Day 8 1000mg, then Cycles 2-6 Day 1 1000mg every 28 days

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

Dosage and administration details:

Fludarabine 25mg/m^2 Days 1-3 every 28 days for 6 cycles

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

Dosage and administration details:

Cyclophosphamide 250 mg/m2 Days 1-3 every 28 days for 6 cycles

Arm title	Fludarabine + Cyclophosphamide_ ITT subjects

Arm description:

Participants with relapsed CLL received IV infusions of fludarabine administered at 25 mg/m^2 and cyclophosphamide administered at 250mg/m^2 on Days 1-3 of each cycle (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

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

Dosage and administration details:

Fludarabine 25mg/m^2 Days 1-3 every 28 days for 6 cycles

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

Dosage and administration details:

Cyclophosphamide 250 mg/m2 Days 1-3 every 28 days for 6 cycles

Number of subjects in period 3	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects
Started	96	89
Completed	87	73
Not completed	9	16
w/drew consent, no f/u, or MD choice	9	16

Baseline characteristics

Reporting groups

Reporting group title	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects

Reporting group description:

Participants with relapsed CLL received IV infusions of ofatumumab in combination with fludarabine and cyclophosphamide IV infusions for 6 cycles; each cycle comprised of 28 days. Participants received ofatumumab administered at 300 milligram (mg) on Day 1, 1000 mg on Day 8 of cycle 1 and 1000 mg on Day 1 of cycles 2, 3, 4, 5 and 6. Fludarabine was administered at 25 mg/meter squared [m^2] and cyclophosphamide was administered at 250mg/m^2 on Days 1-3 of each cycles (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Reporting group title	Fludarabine + Cyclophosphamide_ ITT subjects

Reporting group description:

Participants with relapsed CLL received IV infusions of fludarabine administered at 25 mg/m^2 and cyclophosphamide administered at 250mg/m^2 on Days 1-3 of each cycle (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Reporting group values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects	Total
Number of subjects	183	182	365
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)	121	110	231
From 65-84 years	62	71	133
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	61.4	61.6	
standard deviation	± 8.82	± 10.21	-
Sex: Female, Male Units: Subjects			
Female	79	66	145
Male	104	116	220
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	3	5	8
American Indian or Alaska Native	3	1	4
Asian - Central/South Asian Heritage	13	16	29
Asian - East Asian Heritage	3	3	6
Asian - South East Asian Heritage	3	3	6

White - Arabic/North African Heritage	0	1	1
White - White/Caucasian/European Heritage	158	153	311
AgeContinuous			
Units: Years			
arithmetic mean	61.4	61.6	
standard deviation	± 8.82	± 10.21	-

End points

End points reporting groups

Reporting group title	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects

Reporting group description:

Participants with relapsed CLL received IV infusions of ofatumumab in combination with fludarabine and cyclophosphamide IV infusions for 6 cycles; each cycle comprised of 28 days. Participants received ofatumumab administered at 300 milligram (mg) on Day 1, 1000 mg on Day 8 of cycle 1 and 1000 mg on Day 1 of cycles 2, 3, 4, 5 and 6. Fludarabine was administered at 25 mg/meter squared [m^2] and cyclophosphamide was administered at 250mg/m^2 on Days 1-3 of each cycles (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Reporting group title	Fludarabine + Cyclophosphamide_ ITT subjects

Reporting group description:

Participants with relapsed CLL received IV infusions of fludarabine administered at 25 mg/m^2 and cyclophosphamide administered at 250mg/m^2 on Days 1-3 of each cycle (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Reporting group title	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects

Reporting group description:

Participants with relapsed CLL received IV infusions of ofatumumab in combination with fludarabine and cyclophosphamide IV infusions for 6 cycles; each cycle comprised of 28 days. Participants received ofatumumab administered at 300 milligram (mg) on Day 1, 1000 mg on Day 8 of cycle 1 and 1000 mg on Day 1 of cycles 2, 3, 4, 5 and 6. Fludarabine was administered at 25 mg/meter squared [m^2] and cyclophosphamide was administered at 250mg/m^2 on Days 1-3 of each cycles (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Reporting group title	Fludarabine + Cyclophosphamide_ ITT subjects

Reporting group description:

Participants with relapsed CLL received IV infusions of fludarabine administered at 25 mg/m^2 and cyclophosphamide administered at 250mg/m^2 on Days 1-3 of each cycle (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Reporting group title	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects

Reporting group description:

Participants with relapsed CLL received IV infusions of ofatumumab in combination with fludarabine and cyclophosphamide IV infusions for 6 cycles; each cycle comprised of 28 days. Participants received ofatumumab administered at 300 milligram (mg) on Day 1, 1000 mg on Day 8 of cycle 1 and 1000 mg on Day 1 of cycles 2, 3, 4, 5 and 6. Fludarabine was administered at 25 mg/meter squared [m^2] and cyclophosphamide was administered at 250mg/m^2 on Days 1-3 of each cycles (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Reporting group title	Fludarabine + Cyclophosphamide_ ITT subjects

Reporting group description:

Participants with relapsed CLL received IV infusions of fludarabine administered at 25 mg/m^2 and cyclophosphamide administered at 250mg/m^2 on Days 1-3 of each cycle (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Subject analysis set title	Ofatumumab+Fludarabine+Cyclophosphamide_anti-CLL therapies
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants with relapsed CLL received IV infusions of ofatumumab in combination with fludarabine and cyclophosphamide IV infusions for 6 cycles; each cycle comprised of 28 days. Participants received ofatumumab administered at 300 milligram (mg) on Day 1, 1000 mg on Day 8 of cycle 1 and 1000 mg on Day 1 of cycles 2, 3, 4, 5 and 6. Fludarabine was administered at 25 mg/meter squared [m^2] and cyclophosphamide was administered at 250mg/m^2 on Days 1-3 of each cycles (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Subject analysis set title	Fludarabine+Cyclophosphamide_anti-CLL therapies

Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants with relapsed CLL received IV infusions of fludarabine administered at 25 mg/m^2 and cyclophosphamide administered at 250mg/m^2 on Days 1-3 of each cycle (6 cycles). Participants were followed up one month post therapy and every 3 months for 5 years to evaluate survival and disease status.

Primary: Progression-free survival (PFS), as assessed by the Independent Review Committee (IRC)

End point title	Progression-free survival (PFS), as assessed by the Independent Review Committee (IRC)

End point description:

PFS is defined as the interval of time between the date of randomization and the earlier of the date of disease progression (progressive disease,PD) and the date of death due to any cause. PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlargerd lymph nodes (>1.5 cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia (CLL).

End point type	Primary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Months				
median (confidence interval 95%)	28.94 (22.80 to 35.88)	18.83 (14.42 to 25.82)		

Statistical analyses

Statistical analysis title	PFS as assessed by the IRC
Comparison groups	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects v Fludarabine + Cyclophosphamide_ ITT subjects
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0032
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.88

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival is defined as the time from randomization to death due to any cause. Each participant was followed at the time when the last IRC-assessed PFS events occurred. Participants who had not died were censored at the date of last contact.

End point type	Secondary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Months				
median (confidence interval 95%)	62.65 (44.58 to 999)	46.23 (37.72 to 56.57)		

Statistical analyses

Statistical analysis title	PFS as assessed by IRC
Comparison groups	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects v Fludarabine + Cyclophosphamide_ ITT subjects
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1427
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.09

Secondary: Time to response, as assessed by the IRC

End point title	Time to response, as assessed by the IRC

End point description:

Time to response is defined as the time from randomization to the first response. Complete Response/remission(CR) all the criteria at least 2 months after last treatment: no lymphadenopathy(Ly) > 1.5 cm/ hepatomegaly/spleenomegaly/constitutional symptoms; neutrophils >1500 per microliter(µL), platelets(PL) >100,000/µL, hemoglobin(Hb) >11 grams/deciliter(g/dL), lymphocytes(LC) <4000/µL, bone marrow(BM) sample must be normocellular for age, <30% LC, no lymphoid nodule. Incomplete bone marrow recovery(CRi): CR criteria, persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. Partial Remission/response(PR): >=50% decrease in LC, Ly, size of liver and spleen and at least one of the following results: PL >100,000/µL or 50% improvement over Baseline(BL), Hb >11 g/dL or 50% improvement over BL. Nodular PR(nPR): persistent nodules BM.

End point type	Secondary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	123		
Units: Months				
median (confidence interval 95%)	0.99 (0.95 to 1.08)	0.99 (0.95 to 1.18)		

Statistical analyses

Statistical analysis title	Time to response as assessed by IRC
Comparison groups	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects v Fludarabine + Cyclophosphamide_ ITT subjects
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.449
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.37

Secondary: Duration of Response (DOR), as assessed by the IRC

End point title	Duration of Response (DOR), as assessed by the IRC

End point description:

DOR is defined as the time from the initial response (CR, CRi, nPR, or PR) to the first documented sign of PD or death due to any cause. PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlargerd lymph nodes (>1.5 cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia.

End point type	Secondary

End point timeframe:

From time of initial response to disease progression or death, whichever came first (up to 5 years after the last dose of study drug)

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	123		
Units: Months				
median (confidence interval 95%)	29.63 (25.03 to 41.46)	24.90 (18.99 to 28.12)		

Statistical analyses

Statistical analysis title	Duration of Response as assessed by the IRC
Comparison groups	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects v Fludarabine + Cyclophosphamide_ ITT subjects
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0878
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.05

Secondary: Time to progression, as assessed by the IRC

End point title	Time to progression, as assessed by the IRC

End point description:

Time to progression is defined as the time from the date of randomization to PD. PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlargerd lymph nodes (>1.5 cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia.

End point type	Secondary

End point timeframe:

From randomization up to 5 years after the last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Months				
median (confidence interval 95%)	42.12 (28.94 to 47.67)	26.78 (22.51 to 31.87)		

Statistical analyses

Statistical analysis title	Time to progression as assessed by the IRC
Comparison groups	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects v Fludarabine + Cyclophosphamide_ ITT subjects
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0036
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.87

Secondary: Time to next therapy

End point title	Time to next therapy

End point description:

Time to next therapy is defined as the time from randomization until the start of the next-line of

treatment. Data are presented for participants who took anti-cancer therapies and participants in the ITT population.

End point type	Secondary

End point timeframe:

From the start of study drug until the start of the next anti-CLL therapy (up to 5 years after the last dose of study drug)

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects	Ofatumumab+ Fludarabine+Cyclophosphamide_anti-CLL therapies	Fludarabine+Cyclophosphamide_anti-CLL therapies
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	183	182	74	67
Units: Months				
median (confidence interval 95%)	52.96 (43.56 to 62.98)	40.08 (32.85 to 48.39)	29.68 (24.97 to 32.66)	21.03 (16.79 to 28.35)

Statistical analyses

Statistical analysis title	Time to next therapy
Comparison groups	Ofatumumab+Fludarabine+Cyclophosphamide_anti-CLL therapies v Fludarabine+Cyclophosphamide_anti-CLL therapies
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0109
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.94

Statistical analysis title	Time to next therapy
Comparison groups	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects v Fludarabine + Cyclophosphamide_ ITT subjects
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1143
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.08

Secondary: Number of participants with improvement in Eastern Cooperative Oncology Group (ECOG) performance status

End point title	Number of participants with improvement in Eastern Cooperative Oncology Group (ECOG) performance status

End point description:

The ECOG performance status scales and criteria are used by doctors and researchers to assess how a participant's disease is progressing, how the disease affects the daily living, and determines appropriate treatment and prognosis. ECOG performance status are measured at Cycle 2 Day1, Cycle 3 Day1, Cycle 4 Day1, Cycle 5 Day1 and Cycle 6 Day1. During follow period, 1 M after study drug therapy, then every 3 month up to 5 year (up to 60 months). Improvement is defined as a decrease from baseline by at least one step on the ECOG performance status scale (yes/no).

End point type	Secondary

End point timeframe:

Cycle 2 Day1, Cycle 3 Day1, Cycle 4 Day1, Cycle 5 Day1, Cycle 6 Day1, follow up (FU) at 1Month (M) after study drug therapy, 3M, then every 3 month up to 5 year (up to 60 months)

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Participants				
Cycle 2 Day 1, n= 170, 168|	15	13		
Cycle 3 Day 1, n= 165,157|	16	13		
Cycle 4 Day 1, n= 153, 132|	19	13		
Cycle 5 Day 1, n= 135, 118|	20	15		
Cycle 6 Day 1, n= 120, 96|	26	16		
1 M, FU, n= 159, 145|	31	22		
3 M, FU, n= 152, 119|	31	21		
6 M, FU, n= 136, 104|	30	18		
9 M, FU, n= 127, 96|	31	23		
12 M, FU, n= 118, 87|	30	20		
15 M, FU, n= 102, 70|	23	18		
18 M, FU, n= 96 ,65|	23	18		
21 M, FU, n= 92, 59|	22	16		
24 M, FU, n= 80, 53|	20	15		
27 M, FU, n= 74, 44|	15	13		
30 M, FU, n= 69, 35|	14	8		
33 M, FU, n= 65, 29|	15	7		
36 M, FU, n= 58, 23|	12	7		
39 M, FU, n= 51, 18|	12	7		
42 M, FU, n= 44, 16|	11	6		

45 M, FU, n= 39, 14|	8	4		
48 M, FU, n= 37, 12|	8	2		
51 M, FU, n= 32, 12|	7	3		
54 M, FU, n= 30, 9|	7	2		
57 M, FU, n= 26, 9|	3	3		
60 M, FU, n= 26, 8|	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with no B-Symptoms or at least one B-symptoms over the time

End point title	Number of Participants with no B-Symptoms or at least one B-symptoms over the time

End point description:

Participants with no B-symptoms (B-Sy) (no night sweat, no weight loss, no fever and no extreme fatigue) and at least one indicated B-sy(night sweats, weight loss, fever or extreme fatigue) were presented at Screening, Cycle 1 Day 1, Cycle 2 Day1, Cycle 3 Day1, Cycle 4 Day1, Cycle 5 Day1, Cycle 6 Day 1 and during follow up period at 1 M after study drug therapy, then every 3 M up to 5 year (up to 60 months).

End point type	Secondary

End point timeframe:

Screening, Cycle1 Day 1, Cycle 2 Day1, Cycle 3 Day1, Cycle 4 Day1, Cycle 5 Day1, Cycle 6 Day 1 and During at 1M after study drug therapy, 3M, then every 3 M up to 5 year (up to 60 months)

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Participants				
Cycle 5 Day 1, no B-sy, n= 134, 118|	120	97		
36 M, FU, no B-sy, n=58, 23|	56	23		
Screening, no B-sy, n= 183, 180|	63	59		
Screening, one B-sy, n= 183, 180|	120	121		
Cycle 1 Day 1, no B-sy, n= 179, 179|	64	68		
Cycle 1 Day 1, one B-sy, n= 179, 179|	115	111		
Cycle 2 Day 1,no B-sy, n= 168, 170|	116	108		
Cycle 2 Day 1, one B-sy, n= 168, 170|	52	62		
Cycle 3 Day 1, no B-sy, n= 165, 156|	131	116		
Cycle 3 Day 1, one B-sy, n= 165, 156|	34	40		
Cycle 4 Day 1, no B-sy, n= 154, 132|	129	107		
Cycle 4 Day 1, one B-sy, n= 154, 132|	25	25		
Cycle 5 Day 1, one B-sy, n= 134, 118|	14	21		
Cycle 6 Day 1, no B-sy, n= 120, 95|	111	82		
Cycle 6 Day 1, one B-sy, n= 120, 95|	9	13		

1 M, FU, no B-sy, n= 161, 145|	141	116		
1 M, FU, one B-sy, n= 161, 145|	20	29		
3 M, FU, no B-sy, n= 153, 119|	136	105		
3 M, FU, one B-sy, n= 153, 119|	17	14		
6 M, FU, no B-sy, n= 138, 107|	123	96		
6 M, FU, one B-sy, n= 138, 107|	15	11		
9 M, FU, no B-sy, n= 129, 96|	116	87		
9 M, FU, one B-sy, n= 129, 96|	13	9		
12 M, FU, no B-sy, n= 119, 87|	108	74		
12 M, FU, one B-sy, n= 119, 87|	11	13		
15 M, FU, no B-sy, n= 103, 71|	98	63		
15 M, FU, one B-sy, n= 103, 71|	5	8		
18 M, FU, no B-sy, n= 98, 64|	93	58		
18 M, FU, one B-sy, n= 98, 64|	5	6		
21 M, FU, no B-sy, n= 94, 60|	87	55		
21 M, FU, one B-sy , n= 94, 60|	7	5		
24 M, FU, no B-sy, n= 80, 52|	79	48		
24 M, FU, one B-sy, n= 80, 52|	1	4		
27 M, FU, no B-sy, n= 74, 45|	71	41		
27 M, FU, one B-syn, n= 74, 45|	4	3		
30 M, FU, no B-sy, n= 70, 35|	68	33		
30 M, FU, one B-sy, n= 70, 35|	2	2		
33 M, FU, no B-sy, n= 66, 29|	63	27		
33 M, FU, one B-sy, n= 66, 29|	3	2		
36 M, FU, one B-sy, n=58, 23|	2	0		
39 M, FU, no B-sy, n=52, 18|	49	18		
39 M, FU, one B-sy, n=52, 18|	3	0		
42 M, FU, no B-sy, n=45, 16|	45	16		
42 M, FU, one B-sy, n=45, 16|	0	0		
45 M, FU, no B-sy, n=n=41, 15|	41	14		
45 M, FU, one B-sy, n=41, 15|	0	1		
48 M, FU, no B-sy, n=37, 13|	36	13		
48 M, FU, one B-sy, n=37, 13|	1	0		
51 M, FU, no B-sy, n=32, 12|	32	11		
51 M, FU, one B-sy, n=32, 12|	0	1		
54 M, FU, no B-sy, n=30, 10|	30	10		
54 M, FU, one B-sy, n=30, 10|	0	0		
57 M, FU, no B-sy, n=26, 9|	26	9		
57 M, FU, one B-sy, n=26, 9|	0	0		
60 M, FU, no B-sy, n=25, 9|	24	9		
60 M, FU, one B-sy, n=25, 9|	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with the best Overall Response (OR), as assessed by the IRC

End point title	Percentage of participants with the best Overall Response (OR), as assessed by the IRC

End point description:

OR is defined as the number of participants achieving an objective response (complete response [CR], CR with incomplete bone marrow recovery [CRi], partial response [PR], and nodular PR [nPR]). CR (all the criteria at least 2 months after last treatment): no lymphadenopathy (Ly) > 1.5 cm/ hepatomegaly/ splenomegaly/ constitutional symptoms; neutrophils >1500 per microliter (µL), platelets (PL) >100,000/µL, hemoglobin (Hb) >11 grams/deciliter (g/dL), lymphocytes (LC) <4000/µL, bone marrow (BM) sample must be normocellular for age, <30% LC, no lymphoid nodule. CRi: CR criteria, persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. PR: >=50% decrease in LC, Ly, size of liver and spleen and at least one of the following results: PL >100,000/µL or 50% improvement over Baseline (BL), Hb >11 g/dL or 50% improvement over BL. nPR: persistent nodules BM.

End point type	Secondary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Percentage of participants				
CR|	27	7		
CRi|	2	1		
nPR|	0	0		
PR|	55	59		
Stable disease|	11	28		
Progressive Disease|	0	0		
Not Evaluable|	4	2		
Missing|	1	2		

Statistical analyses

Statistical analysis title	Best OR as assessed by IRC
Comparison groups	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects v Fludarabine + Cyclophosphamide_ ITT subjects
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of participants with the best OR, as assessed by the Investigator

End point title	Percentage of participants with the best OR, as assessed by the Investigator

End point description:

OR is defined as the number of participants achieving an objective response (complete response [CR], CR with incomplete bone marrow recovery [CRi], partial response [PR], and nodular PR [nPR]). CR (all the criteria at least 2 months after last treatment): no lymphadenopathy (Ly) > 1.5 cm/ hepatomegaly/ splenomegaly/ constitutional symptoms; neutrophils >1500 per microliter (µL), platelets (PL) >100,000/µL, hemoglobin (Hb) >11 grams/deciliter (g/dL), lymphocytes (LC) <4000/µL, bone marrow (BM) sample must be normocellular for age, <30% LC, no lymphoid nodule. CRi: CR criteria, persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. PR: >=50% decrease in LC, Ly, size of liver and spleen and at least one of the following results: PL >100,000/µL or 50% improvement over Baseline (BL), Hb >11 g/dL or 50% improvement over BL. nPR: persistent nodules BM. Responder = CR + CRi + NPR + PR

End point type	Secondary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Percentage of participants				
CR|	45	24		
CRi|	12	4		
nPR|	2	8		
PR|	107	113		
Stable disease|	9	21		
Progressive Disease|	0	3		
Missing|	8	9		
Responder|	166	149		

Statistical analyses

Statistical analysis title	Best OR as assessed by Investigator
Comparison groups	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects v Fludarabine + Cyclophosphamide_ ITT subjects
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0166
Method	Cochran-Mantel-Haenszel

Secondary: Number of participants who were negative for Minimal Residual Disease (MRD) assessed by IRC

End point title	Number of participants who were negative for Minimal Residual Disease (MRD) assessed by IRC

End point description:

MRD refers to small number of leukemic cells that remain in the participant during treatment or after treatment at the time the participant achieved a confirmed CR. MRD analysis was performed for the participants who were suspected of achieving a primary endpoint CR. MDR was performed by flow cytometry on a bone marrow or peripheral blood sample taken at least 2 months after final treatment. MRD negative was defined as less than one CLL cell per 10000 leukocytes.

End point type	Secondary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Participants				
Screening, n= 46, 13|	0	0		
Cycle 1 Day 1, n= 2, 0|	0	999		
3 M, FU, n= 44, 12|	21	7		
6 M, FU, n= 35, 11|	25	6		
9 M, FU, n= 29, 8|	20	4		
12 M, FU, n= 25, 4|	16	1		
15 M, FU, n= 20, 3|	14	1		
18 M, FU, n= 16, 2|	12	1		
21 M, FU, n= 13, 2|	9	1		
24 M, FU, n= 9, 2|	8	1		
27 M, FU, n= 9, 1|	8	0		
30 M, FU, n= 9, 2|	8	2		
33 M, FU, n= 5, 2|	3	1		
36 M, FU, n= 5, 2|	5	1		
39 M, FU, n= 2, 1|	2	1		
42 M, FU, n= 2, 0|	2	999		
45 M, FU, n= 1, 1|	1	1		
48 M, FU, n= 2, 1|	2	1		
51 M, FU, n= 2, 1|	2	1		
54 M, FU, n= 2, 1|	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who were negative for MRD assessed by investigator

End point title	Number of participants who were negative for MRD assessed by investigator

End point description:

MRD refers to small number of leukemic cells that remain in the participant during treatment or after

treatment at the time the participant achieved a confirmed CR. MRD analysis was performed for the participants who were suspected of achieving a primary endpoint CR. MDR was performed by flow cytometry on a bone marrow or peripheral blood sample taken at least 2 months after final treatment. MRD negative was defined as less than one CLL cell per 10000 leukocytes.

End point type	Secondary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Participants				
Screening, n= 177, 171|	0	1		
3 M, FU, n= 120, 76|	39	15		
6 M, FU, n= 87, 57|	48	11		
9 M, FU, n= 71, 29|	35	6		
12 M, FU, n= 55, 18|	31	3		
15 M, FU, n= 38, 14|	23	2		
18 M, FU, n= 31, 13|	20	2		
21 M, FU, n= 27, 9|	16	3		
24 M, FU, n= 15, 4|	13	2		
27 M, FU, n= 18, 5|	14	1		
30 M, FU, n= 15, 3|	12	3		
33 M, FU, n= 13, 3|	8	2		
36 M, FU, n= 10, 4|	9	2		
39 M, FU, n= 7, 3|	6	2		
42 M, FU, n= 8, 1|	7	1		
45 M, FU, n= 7, 2|	6	2		
48 M, FU, n= 6, 3|	6	2		
51 M, FU, n= 6, 2|	5	1		
54 M, FU, n= 7, 2|	4	2		
57 M, FU, n= 4, 3|	3	2		
60 M, FU, n= 3, 3|	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any Adverse Event (AE) or Serious Adverse Event (SAE)

End point title	Number of participants with any Adverse Event (AE) or Serious Adverse Event (SAE)

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury.

End point type	Secondary

End point timeframe:

From first dose of study medication to 60 Days after the last dose of study medication (for an AE), or up to 5 years after the last dose of study drug or until the time of the next anti-CLL therapy (for SAE)

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	178		
Units: Participants				
AE|	170	153		
SAE|	108	86		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Human Anti-human Antibody (HAHA) Positive Result at indicated time points

End point title	Number of Participants With a Human Anti-human Antibody (HAHA) Positive Result at indicated time points

End point description:

Serum samples for analysis of HAHA were collected at Baseline (Screening), after 3 cycles were compelted, after 1 M and 6 M post last dose. All samples were first tested in a screening step; positive samples from the screening were further evaluated in a confirmation test. The confirmed positive samples were reported as HAHA-positive.

End point type	Secondary

End point timeframe:

From start of study drug until 60 days after the last dose of study medication

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	178		
Units: Participants				
Screening Visit, n= 179,177|	8	1		
Cycle 4 Day 1, n= 151,130|	0	2		
1 M, FU, n= 148,132|	0	2		

3 M, FU, n= 0,1|	0	0		
6 M, FU, n= 130, 99|	2	0		
9 M, FU, n= 0, 2|	0	0		
30 M, FU, n= 2, 0|	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Autoimmune Hemolytic Anaemia (AIHA)

End point title	Number of participants with Autoimmune Hemolytic Anaemia (AIHA)

End point description:

AIHA is a condition where the body's immune system fails to recognize red blood cells as "self" and begins destroying these red blood cells. The number of participants experienced AIHA are presented.

End point type	Secondary

End point timeframe:

From first dose of study medication to 60 days after the last dose of study medication (for an AE), or up to 5 years after the last dose of study drug or until the time of the next anti-CLL therapy (for SAE)

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	178		
Units: Participants	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean level of Immunoglobulin (Ig) Antibodies IgA, IgG, and IgM

End point title	Mean level of Immunoglobulin (Ig) Antibodies IgA, IgG, and IgM

End point description:

Immunoglobulins, or antibodies, are large proteins used by the immune system to identify and neutralize foreign particles such as bacteria and viruses. Their normal blood levels indicate proper immune status. Low levels indicate immuno-suppression. Blood samples were collected from each participant and IgA, IgG, and IgM were measured at Baseline, and 1M and 6M after last dose during follow up period.

End point type	Secondary

End point timeframe:

Baseline, 1M and 6M follow up

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	178		
Units: Gram per liter				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, IgA, n= 179, 175|	1.0 (± 0.74)	0.9 (± 0.68)		
Cycle 1 Day 1, IgG, n= 179, 175|	8.7 (± 5.22)	8.2 (± 3.86)		
Cycle 1 Day 1, IgM, n= 179, 175|	0.6 (± 1.36)	0.8 (± 1.77)		
1 M, FU, IgA, n= 150, 131|	1.0 (± 0.79)	1.0 (± 0.77)		
1 M, FU, IgG, n= 150, 131|	7.9 (± 4.05)	7.9 (± 3.38)		
1 M, FU, IgM, n= 150, 131|	0.5 (± 1.16)	0.8 (± 1.88)		
6 M, FU, IgA, n= 130, 101|	1.0 (± 0.77)	1.0 (± 0.76)		
6 M, FU, IgG, n= 130, 101|	7.8 (± 3.97)	8.9 (± 4.31)		
6 M, FU, IgM, n= 130, 101|	0.4 (± 0.50)	1.1 (± 1.98)		
9 M, FU, IgA, n= 1, 2|	0.9 (± 999)	0.9 (± 0.21)		
9 M, FU, IgG, n= 1, 2|	15.2 (± 999)	8.8 (± 6.87)		
9 M, FU, IgM, n= 1, 2|	0.8 (± 999)	0.2 (± 0.04)		
18 M, FU, IgA, n= 0, 1|	999 (± 999)	2.4 (± 999)		
18 M, FU, IgG, n= 0, 1|	999 (± 999)	9.1 (± 999)		
18 M, FU, IgM, n= 0, 1|	999 (± 999)	1.0 (± 999)		
30 M, FU, IgA, n= 2, 0|	1.3 (± 1.17)	999 (± 999)		
30 M, FU, IgG, n= 2, 0|	4.7 (± 0.33)	999 (± 999)		
30 M, FU, IgM, n= 2, 0|	0.4 (± 0.26)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Cluster of Differentiation (CD) Cell Counts, CD5+ and CD19+

End point title	Change from baseline in Cluster of Differentiation (CD) Cell Counts, CD5+ and CD19+

End point description:

CD5+ and CD19+ cells were counted by flow cytometry at Screening (Baseline) on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1 during the treatment period and after last dose of study drug at 1 M and then every three month follow up up to 45 M. Flow cytometry is a technique for counting and examining microscopic particles with an electronic detection apparatus. Baseline is defined as the assessment closest to but prior to first dose (e.g. day 1 if available, otherwise, screening). Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

Screening, Cycle 1 Day1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1 and after last dose at 1 M and then every three months up to 45 M during Follow-up Period

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: cells/uL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1,n=71, 65|	43180.6 (± 48784.64)	53208.7 (± 70944.56)		
Cycle 1 Day 15, n= 69, 62|	2656.9 (± 6418.02)	9244.0 (± 19610.62)		
Cycle 2 Day 1, n= 68, 63|	2057.4 (± 5525.72)	10318.8 (± 21453.15)		
Cycle 2 Day 15, n= 68, 59|	513.7 (± 1717.65)	6874.4 (± 20632.64)		
Cycle 3 Day 1,n= 68, 59|	790.0 (± 2953.42)	6423.6 (± 19725.57)		
Cycle 4 Day 1, n= 62, 49|	402.1 (± 1768.74)	2643.2 (± 8092.22)		
Cycle 5 Day 1,n= 57, 45|	142.6 (± 472.24)	2838.6 (± 8314.08)		
Cycle 6 Day 1, n= 56, 39|	109.8 (± 398.77)	3862.7 (± 13312.14)		
1 M, FU, n= 64, 61|	163.5 (± 685.41)	5514.3 (± 17369.97)		
3 M, FU, n= 69, 47|	671.3 (± 2786.99)	2604.9 (± 9229.90)		
6 M, FU, n= 61, 42|	1591.6 (± 8857.22)	2275.6 (± 5118.00)		
9 M, FU, n= 56, 37|	910.5 (± 2495.85)	3408.4 (± 7438.45)		
12 M, FU, n= 47, 30|	2303.2 (± 6675.70)	2876.5 (± 6252.53)		
15 M, FU, n= 35, 18|	3325.8 (± 8006.48)	3072.7 (± 9038.23)		
18 M, FU, n= 22, 12|	1607.5 (± 2935.82)	4549.8 (± 8839.23)		
21 M, FU, n= 22, 10|	3830.8 (± 8989.02)	5236.9 (± 10537.31)		
24 M, FU, n= 9, 6|	1244.6 (± 1300.01)	7843.3 (± 11897.55)		
27 M, FU, n= 7, 4|	1877.4 (± 2117.84)	6128.0 (± 9161.38)		
30 M, FU, n= 6, 2|	5029.7 (± 8266.90)	6515.5 (± 5916.36)		
33 M, FU, n= 4, 1|	14166.8 (± 20166.09)	5208.0 (± 999)		
36 M, FU, n= 3, 1|	1187.0 (± 1407.79)	8184.0 (± 999)		
39 M, FU, n=1, 0|	557.0 (± 999)	999 (± 999)		
42 M, FU, n= 1, 0|	1640.0 (± 999)	999 (± 999)		
45 M, FU, n= 2, 0|	4689.0 (± 1493.41)	999 (± 999)		
48 M FU, n= 1, 1|	27755.0 (± 999)	29155.0 (± 999)		

54 M FU, n= 1, 0|	189849.0 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cell Counts, CD5- CD19+

End point title	Change from Baseline in Cell Counts, CD5- CD19+

End point description:

CD5- CD19+ cells were counted by flow cytometry at Screening (baseline) at Cycle 1 Day1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1 during treatment period and after last dose of study drug at 1 M and then every three month up to 45 M during follow up period. Flow cytometry is a technique for counting and examining microscopic particles with an electronic detection apparatus. Baseline is defined as the assessment closest to but prior to first dose (e.g. Day 1 if available otherwise screening). Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

Screening, Cycle 1 Day1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1 and after last dose at 1 M and then every three month up to 45 M during Follow-up Period

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	178		
Units: cells/uL				
arithmetic mean (standard deviation)				
Screening, n= 71, 62|	4817.8 (± 20948.17)	6959.1 (± 39980.14)		
Cycle 1 Day 1,n= 71, 65|	5996.7 (± 22331.29)	2041.3 (± 4418.63)		
Cycle 1 Day 15, n= 69, 62|	239.0 (± 1052.19)	351.7 (± 1377.56)		
Cycle 2 Day 1, n= 68, 63|	115.4 (± 403.09)	465.7 (± 1610.05)		
Cycle 2 Day 15,n= 68, 59|	35.6 (± 133.75)	331.3 (± 1177.18)		
Cycle 3 Day 1,n= 68, 59|	39.5 (± 144.64)	179.7 (± 520.63)		
Cycle 4 Day 1, n= 62, 49|	25.7 (± 92.88)	95.3 (± 369.19)		
Cycle 5 Day 1, n= 57, 45|	15.9 (± 77.11)	195.5 (± 945.34)		
Cycle 6 Day 1, n= 56, 39|	10.0 (± 29.85)	649.7 (± 3606.28)		
1 M, FU, n= 64, 61|	7.5 (± 19.54)	863.8 (± 5001.84)		

3 M, FU, n= 69, 47|	40.1 (± 238.18)	172.0 (± 681.28)		
6 M, FU, n= 61, 42|	21.2 (± 58.16)	50.7 (± 49.13)		
9 M, FU, n= 56, 37|	85.7 (± 359.01)	92.0 (± 101.16)		
12 M, FU, n= 47, 30|	89.9 (± 226.06)	220.1 (± 698.57)		
15 M, FU, n= 35, 18|	67.3 (± 59.52)	94.6 (± 70.17)		
18 M, FU, n= 22, 12|	126.1 (± 188.25)	92.3 (± 69.14)		
21 M, FU, n= 22, 10|	375.5 (± 1307.35)	108.3 (± 95.86)		
24 M, FU, n= 9, 6|	74.0 (± 57.46)	104.5 (± 70.46)		
27 M, FU, n= 7, 4|	73.9 (± 60.40)	187.5 (± 200.85)		
30 M, FU, n= 6, 2|	74.2 (± 58.82)	129.5 (± 5303)		
33 M, FU, n= 4, 1|	41.8 (± 40.13)	1003.0 (± 999)		
36 M, FU, n= 3, 1|	107.3 (± 86.75)	1506.0 (± 999)		
39 M, FU, n= 1, 0|	13.0 (± 999)	999 (± 999)		
42 M, FU, n= 1, 0|	13.0 (± 999)	999 (± 999)		
45 M, FU, n= 2, 0|	166.5 (± 222.74)	999 (± 999)		
48 M, FU, n= 1,1|	6528.0 (± 999)	28.0 (± 999)		
54 M, FU, n= 1, 0|9	690.0 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Prognostic and biological markers correlating with clinical response

End point title	Prognostic and biological markers correlating with clinical response

End point description:

Blood samples were collected for the assessment of the following prognostic markers at BL: immunoglobulin heavy chain variable region(IgVH) homology; Zeta-Chain-Associated Protein Kinase 70(ZAP70), VH3-21 usage; Cytogenetics (by fluorescent in situ hybridization [FISH]); beta 2 microglobulin. Cox-regression model was used to explore the relationship between progression-free survival and the following explanatory variables: treatment group, cytogenetics (analyzed by FISH included 6q-,11q-, +12q, 17p-, 13q-) , ZAP-70 (positive, negative or intermediate), VH3-21 usage (Yes and No), IgVH homology (>98%, 97%-98% and <97%), beta 2 microglobulin (>3500 microgram per liter [µg/L] and <=3500 µg/L). For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested compared with the other effects tested. Cytogenetics Group (based on >=20%)=cytogenetics (CY G).

End point type	Secondary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Participants				
B2 Microglobulin G 1: > 3500 µg/L	79	78		
B2 Microglobulin G 1: ≤3500 µg/L, n=51,47|	22	26		
CY G 1: 11q-, n=40, 31|	29	19		
CY G 1: 17p-, n=7, 13|	6	9		
CY G 1: 6q- or +12q or 13q-, n=84, 80|	38	48		
CY G 1: no aberration, n=45, 47|	27	27		
VH3-21 Usage Flag: Yes, n=9, 7|	6	4		
VH3-21 Usage Flag: No, n=159, 162|	93	96		
IgVH Homology, <97%, n=40, 43|	13	15		
IgVH Homology, 97%-98%, n=12, 10|	5	7		
IgVH Homology, >98%, n=115, 116|	80	78		
ZAP70 G 1, Negative, n=28, 32|	14	13		
ZAP70 G 1, Intermediate, n=54, 46|	27	23		
ZAP70, G1 Positive, n=94, 91|	60	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Patient Reported Outcome (PRO) measures and scores for European organization for research and treatment of cancer quality of life questionnaire, chronic lymphocytic leukaemia 16 item module (EORTC QLQ-CLL 16)

End point title	Changes in Patient Reported Outcome (PRO) measures and scores for European organization for research and treatment of cancer quality of life questionnaire, chronic lymphocytic leukaemia 16 item module (EORTC QLQ-CLL 16)

End point description:

The EORTC QLQ-CLL16 is comprised of 16 questions that address 5 domains of health-related quality of life (HRQoL) important in CLL. There are 4 multi-item scales – fatigue (2 items), treatment side effects ([TSE], 4 items), disease symptoms (disease effects scale [DES], 4 items), and infection scale [IS] (4 items) – and single item scales (social activities [Social Problems (SP) Scale] and future health worries[Future Health (FH) Scale].). These are measured on a four point scale where 1 = not at all and 4 = very much. These scores are transformed to give a rating from 0 – 100, where 0 =no symptoms or problems and 100 = a severe symptoms or problems. EORTC QLQ-CLL16 was assessed at Screening; Cycle 4 Day 1 and during follow-up 1 M and every 3 M up to 24 months. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The Baseline value was obtained at randomization.

End point type	Secondary

End point timeframe:

Screening, Cycle 3 Day 1, and 1 M and every 3 month post last dose up to 24 month.

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: scores on a scale				
arithmetic mean (standard deviation)				
FH, 18 M, FU, n=90, 58|	-15.9 (± 31.69)	-18.4 (± 33.72)		
DES, Cycle 4 Day 1, n=142,125|	-8.5 (± 18.08)	-9.0 (± 17.16)		
DES, 1 M, FU, n=138, 123|	-9.7 (± 19.18)	-9.8 (± 19.89)		
DES, 3 M, FU, n=145, 109|	-8.2 (± 19.48)	-10.9 (± 19.07)		
DES, 6 M, FU, n= 126, 99|	-9.8 (± 17.99)	-11.6 (± 18.05)		
DES, 9 M, FU, n=115, 85|	-8.2 (± 20.70)	-12.0 (± 17.04)		
DES. 12 M, FU, n=109, 76|	-10.1 (± 18.64)	-10.2 (± 16.09)		
DES, 15 M, FU, n=98, 62|	-8.6 (± 18.08)	-10.2 (± 16.91)		
DES, 18 M, FU, n=90, 59|	-8.5 (± 18.53)	-11.6 (± 18.79)		
DES, 21 M, FU, n=87, 53|	-8.2 (± 18.48)	-11.3 (± 17.60)		
DES, 24 M, FU, n=70, 50|	-7.1 (± 19.93)	-13.6 (± 16.18)		
Fatigue Scale (FS), Cycle 4 Day 1, n=142, 125|	-7.0 (± 22.57)	-7.1 (± 24.16)		
FS, 1 M, FU, n=139, 123|	-5.4 (± 29.16)	-6.2 (± 28.74)		
FS, 3 M, FU, n=144, 109|	-4.4 (± 26.30)	-8.3 (± 30.14)		
FS, 6 M, FU, n=126, 99|	-7.1 (± 25.94)	-12.0 (± 25.98)		
FS, 9 M, FU, n= 115, 85|	-6.2 (± 27.08)	-10.6 (± 26.95)		
FS. 12 M, FU, n=109, 76|	-7.3 (± 27.26)	-8.1 (± 25.75)		
FS, 15 M, FU, n=97, 62|	-7.6 (± 22.57)	-9.9 (± 24.04)		
FS, 18 M, FU, n=90,59|	-7.0 (± 23.03)	-3.7 (± 33.34)		
FS, 21 M, FU, n=87, 53|	-10.3 (± 24.28)	-8.2 (± 27.27)		
FS, 24 M, FU, n=69, 50|	-8.7 (± 24.19)	-8.7 (± 25.48)		
FH, Cycle 4 Day 1, n=141, 123|	-11.8 (± 32.89)	-10.6 (± 27.76)		
FH, 1 M, FU, n=139, 120|	-15.3 (± 35.04)	-11.9 (± 29.56)		
FH, 3 M, FU, n=145, 107|	-14.3 (± 33.96)	-14.0 (± 32.06)		
FH, 6 M, FU, n=126, 96|	-13.4 (± 33.98)	-17.7 (± 30.57)		
FH, 9 M, FU, n=113, 81|	-15.6 (± 33.65)	-13.2 (± 34.43)		
FH. 12 M, FU, n=109, 74|	-14.1 (± 32.80)	-14.9 (± 33.63)		
FH, 15 M, FU, n=98, 61|	-14.6 (± 29.14)	-14.2 (± 34.13)		
FH, 21 M, FU, n=87, 52|	-16.9 (± 28.70)	-15.4 (± 29.12)		

FH, 24 M, FU, n=70, 49|	-21.0 (± 29.58)	-17.7 (± 30.51)		
IS, Cycle 4 Day 1, n=142,125|	0.5 (± 17.65)	-1.4 (± 18.23)		
IS, 1 M, FU, n=138, 122|	2.9 (± 22.79)	2.7 (± 24.06)		
IS, 3 M, FU, n=144, 109|	0.8 (± 19.42)	0.8 (± 20.99)		
IS, 6 M, FU, n=126, 99|	-1.2 (± 18.46)	-0.9 (± 20.40)		
IS, 9 M, FU, n=115, 85|	-1.4 (± 18.81)	1.4 (± 22.45)		
IS. 12 M, FU, n=109, 76|	0.4 (± 19.22)	2.1 (± 20.92)		
IS, 15 M, FU, n=97, 60|	0.5 (± 17.56)	0.3 (± 18.79)		
IS, 18 M, FU, n=89, 59|	-2.0 (± 16.04)	0.9 (± 19.04)		
IS, 21 M, FU, n=87, 53|	-2.5 (± 18.13)	2.5 (± 22.09)		
IS, 24 M, FU, n=69, 49|	-0.5 (± 18.85)	0.5 (± 21.34)		
SP Scale Cycle 4 Day 1, n=141, 125|	1.9 (± 25.44)	0.3 (± 26.94)		
SP Scale, 1 M, FU, n=137, 121|	3.2 (± 34.51)	0.0 (± 35.22)		
SP Scale, 3 M, FU, n=143, 109|	-1.9 (± 33.04)	-4.3 (± 35.75)		
SP Scale, 6 M, FU, n=124, 98|	-5.6 (± 31.73)	-10.9 (± 30.56)		
SP Scale, 9 M, FU, n=114, 85|	-5.0 (± 30.15)	-11.0 (± 31.45)		
SP Scale. 12 M, FU, n=107, 75|	-7.2 (± 31.06)	-7.6 (± 34.47)		
SP Scale, 15 M, FU, n=95, 61|	-6.7 (± 30.21)	-13.7 (± 30.05)		
SP Scale, 18 M, FU, n=89, 59|	-7.1 (± 31.57)	-8.5 (± 40.40)		
SP Scale, 21 M, FU, n=86, 53|	-8.1 (± 31.07)	-7.5 (± 37.92)		
SP Scale, 24 M, FU, n=68, 50|	-11.8 (± 24.27)	-8.7 (± 36.15)		
TSE, Cycle 4 Day 1, n=142, 125|	-4.7 (± 16.15)	-4.0 (± 16.78)		
TSE, 1 M, FU, n=139, 123|	-5.0 (± 18.09)	-3.2 (± 19.08)		
TSE, 3 M, FU, n=145,109|	-3.7 (± 19.41)	-4.3 (± 17.03)		
TSE, 6 M, FU, n=126, 99|	-6.0 (± 15.25)	-4.8 (± 16.96)		
TSE, 9 M, FU, n=115, 85|	-4.3 (± 17.22)	-5.1 (± 16.38)		
TSE. 12 M, FU, n=109, 76|	-5.2 (± 16.44)	-3.2 (± 13.94)		
TSE, 15 M, FU, n=98, 62|	-4.0 (± 14.92)	-4.2 (± 13.73)		
TSE, 18 M, FU, n=90, 60|	-4.4 (± 17.10)	-3.6 (± 19.18)		
TSE, 21 M, FU, n=87, 54|	-4.7 (± 16.63)	-4.0 (± 15.91)		
TSE, 24 M, FU, n=70, 50|	-5.4 (± 17.52)	-6.5 (± 14.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient Reported Outcome (PRO) as assessed by EuroQoL Five-Dimension (EQ-5D) score at indicated visit

End point title	Change from Baseline in Patient Reported Outcome (PRO) as assessed by EuroQoL Five-Dimension (EQ-5D) score at indicated visit

End point description:

EQ-5D is comprised of a 5-item health status measure and a visual analogue scale (VAS) and is used to generate two scores: the utility score and the thermometer score. The utility score measures mobility, self-care, usual activities, pain, discomfort, and anxiety/depression. Responses to each of the 5 health states are measured on a 3-point scale (level 1 = no problem; level 2 = some or moderate problem(s) and level 3 = unable, or extreme problems). Responses are typically converted into health utilities or valuations on a scale ranging from 0 (death) to 1 (perfect health). The thermometer score ranges from

0 (worst imaginable health state) to 100 (best imaginable health state). Change from Baseline was calculated as the post-Baseline value minus the Baseline value. A Negative health status describes health state worse than death.Baseline is the most recent, non-missing value prior to or on the first study drug dose date.

End point type	Secondary

End point timeframe:

Screening, Cycle 3 Day 1, and 1 M and every 3 month post last dose up to 24 month.

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Score on a scale				
arithmetic mean (standard deviation)				
UT, Cycle 4 Day 1, n=136, 121|	0.0 (± 0.27)	0.0 (± 0.21)		
UT, 1 M, FU, n=133, 117|	0.1 (± 0.22)	0.0 (± 0.28)		
UT, 3 M, FU, n=141, 102|	0.0 (± 0.27)	0.1 (± 0.23)		
UT, 6 M, FU, n=122, 96|	0.1 (± 0.24)	0.1 (± 0.24)		
UT, 9 M, FU, n=110, 81|	0.1 (± 0.26)	0.1 (± 0.24)		
UT. 12 M, FU, n=107, 71|	0.1 (± 0.21)	0.1 (± 0.22)		
UT, 15 M, FU, n=96, 58|	0.0 (± 0.23)	0.1 (± 0.24)		
UT, 18 M, FU, n=88, 57|	0.1 (± 0.21)	0.0 (± 0.34)		
UT, 21 M, FU, n= 87, 52|	0.1 (± 0.21)	0.1 (± 0.26)		
UT, 24 M, FU, n=68, 47|	0.1 (± 0.19)	0.1 (± 0.28)		
VAS Cycle 4 Day 1, n=137, 122|	6.1 (± 17.68)	5.6 (± 17.64)		
VAS, 1 M, FU, n=138, 122|	5.6 (± 20.73)	5.9 (± 22.83)		
VAS, 3 M, FU, n=141, 107|	5.7 (± 19.92)	9.6 (± 20.88)		
VAS, 6 M, FU, n=124, 99|	8.2 (± 18.84)	11.1 (± 19.08)		
VAS, 9 M, FU, n=114, 85|	8.1 (± 18.33)	11.9 (± 20.59)		
VAS. 12 M, FU, n=108, 75|	7.0 (± 21.93)	10.3 (± 21.21)		
VAS, 15 M, FU, n=95, 62|	8.0 (± 17.52)	13.1 (± 21.06)		
VAS, 18 M, FU, n=89, 60|	9.4 (± 17.86)	11.1 (± 25.40)		
VAS, 21 M, FU, n=87, 53|	8.1 (± 16.42)	11.3 (± 24.16)		
VAS, 24 M, FU, n=69, 50|	8.8 (± 19.50)	15.2 (± 21.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the European organization for the research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30) score

End point title	Change from baseline in the European organization for the research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30) score

End point description:

EORTC QLQ-C30, a self-reported, cancer-specific instrument assessing 15 domains: physical, role,

emotional, cognitive and social functioning, pain,fatigue, nausea and vomiting, insomnia, loss of appetite, constipation, diarrhea, and dyspnea, financial difficulties and a global health status/quality of life (QOF). Functional and symptoms scales were measured on four point Likert scale where 1 = not at all and 4 = very much. Pat. assessed at Screening; Cycle 4 Day 1 and during follow-up 1 M and every 3 M up to 24 months. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Baseline is the most recent, non-missing value prior to or on the first study treatment dose date. Clinically meaningful changes or minimally important differences (MIDs)have been previously established for the EORTC QLQ C30, and categorized as 'small' if the mean change in scores is 5-10 points, 'moderate' if 10-20 points, and 'large' if >20points.

End point type	Secondary

End point timeframe:

Screening, Cycle 3 Day 1, and 1 M and every 3 month post last dose up to 24 month.

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Diarrhoea, 6 M, FU, n=124, 98|	0.0 (± 20.38)	-3.1 (± 16.64)		
Financial Difficulties, 6 M, FU, n=126, 98|	-5.8 (± 24.61)	-8.8 (± 26.89)		
Global Health Status, 6 M, FU, n=125, 97|	7.5 (± 21.57)	13.7 (± 23.01)		
Appetite Loss, Cycle 4 Day 1, n=140, 124|	0.5 (± 25.60)	-1.9 (± 26.65)		
Appetite Loss, 1 M, FU, n=136, 119|	-0.2 (± 26.14)	-3.9 (± 28.52)		
Appetite Loss, 3 M, FU, n=142, 108|	-0.7 (± 26.77)	-7.4 (± 28.22)		
Appetite Loss, 6 M, FU, n=123, 97|	-6.0 (± 23.00)	-12.4 (± 26.05)		
Appetite Loss, 9 M, FU, n=112, 83|	-3.9 (± 20.38)	-9.6 (± 25.25)		
Appetite Loss. 12 M, FU, n=107, 72|	-4.0 (± 22.76)	-6.0 (± 27.59)		
Appetite Loss, 15 M, FU, n=96, 60|	-3.8 (± 23.13)	-9.4 (± 28.19)		
Appetite Loss, 18 M, FU, n=89, 60|	-7.9 (± 20.11)	-9.4 (± 30.12)		
Appetite Loss, 21 M, FU, n=87, 52|	-3.4 (± 20.36)	-7.7 (± 27.70)		
Appetite Loss, 24 M, FU, n=69, 48|	-3.9 (± 22.53)	-12.5 (± 29.68)		
Cognitive Functioning, Cycle 4 Day 1, n=142, 126|	3.4 (± 18.25)	2.5 (± 18.39)		
Cognitive Functioning, 1 M, FU, n=139, 122|	-0.4 (± 18.40)	3.0 (± 19.87)		
Cognitive Functioning, 3 M, FU, n= 145, 109|	0.0 (± 18.74)	2.3 (± 21.69)		
Cognitive Functioning, 6 M, FU, n=126, 99|	1.7 (± 18.95)	2.7 (± 20.99)		
Cognitive Functioning, 9 M, FU, n=115, 85|	-0.6 (± 20.58)	2.4 (± 19.61)		
Cognitive Functioning. 12 M, FU, n=110, 76|	-2.1 (± 19.17)	-1.8 (± 21.36)		
Cognitive Functioning, 15 M, FU, n=97, 62|	-1.0 (± 17.97)	0.3 (± 20.58)		
Cognitive Functioning, 18 M, FU, n=89, 61|	-0.9 (± 20.00)	-0.3 (± 22.67)		

Cognitive Functioning, 21 M, FU, n=88, 53|	-1.9 (± 21.65)	-1.9 (± 21.84)		
Cognitive Functioning, 24 M, FU, n=70, 50|	1.0 (± 20.83)	-1.3 (± 21.25)		
Constipation, Cycle 4 Day 1, n=142, 126|	2.1 (± 21.46)	0.8 (± 18.60)		
Constipation, 1 M, FU, n=139, 122|	-0.7 (± 19.02)	0.3 (± 18.92)		
Constipation, 3 M, FU, n= 145, 109|	-2.1 (± 19.33)	-0.9 (± 20.01)		
Constipation, 6 M, FU, n=125, 98|	-3.5 (± 19.32)	0.3 (± 18.22)		
Constipation, 9 M, FU, n=115, 85|	-1.2 (± 19.71)	0.4 (± 18.18)		
Constipation. 12 M, FU, n=109, 76|	-0.0 (± 23.13)	0.4 (± 19.24)		
Constipation, 15 M, FU, n=96, 62|	-1.7 (± 21.29)	-3.8 (± 20.11)		
Constipation, 18 M, FU, n=90, 61|	-0.4 (± 21.49)	-1.1 (± 24.32)		
Constipation, 21 M, FU, n=87, 53|	-1.9 (± 22.93)	-3.8 (± 23.26)		
Constipation, 24 M, FU, n=70, 50|	0.0 (± 21.23)	-3.3 (± 21.56)		
Diarrhoea, Cycle 4 Day 1,n= 141, 125|	0.2 (± 19.72)	-2.4 (± 17.54)		
Diarrhoea, 1 M, FU, n=135, 121|	-3.5 (± 20.87)	0.8 (± 21.28)		
Diarrhoea, 3 M, FU, n=143, 109|	1.6 (± 22.49)	1.5 (± 20.98)		
Diarrhoea, 9 M, FU, n=114, 85|	0.3 (± 20.56)	-2.7 (± 17.97)		
Diarrhoea. 12 M, FU, n=108, 76|	-3.4 (± 15.75)	-2.2 (± 19.12)		
Diarrhoea, 15 M, FU, n=96, 61|	-1.7 (± 19.57)	-4.4 (± 20.62)		
Diarrhoea, 18 M, FU, n=89, 61|	-1.9 (± 17.67)	-1.1 (± 17.18)		
Diarrhoea, 21 M, FU, n=87, 53|	-2.3 (± 18.88)	0.6 (± 21.17)		
Diarrhoea, 24 M, FU, n=68, 50|	-2.9 (± 17.02)	-0.7 (± 20.75)		
Dyspnoea Cycle 4 Day 1,n= 138, 124|	-4.6 (± 22.85)	-4.6 (± 23.41)		
Dyspnoea, 1 M, FU, n=139, 121|	-1.0 (± 26.60)	-2.8 (± 25.67)		
Dyspnoea, 3 M, FU, n=141, 108|	-3.1 (± 26.40)	-1.5 (± 25.53)		
Dyspnoea, 6 M, FU, n=124, 97|	-2.7 (± 21.92)	-7.2 (± 24.17)		
Dyspnoea, 9 M, FU, n=113, 83|	-2.7 (± 26.03)	-6.4 (± 23.55)		
Dyspnoea. 12 M, FU, n=108, 73|	-3.4 (± 24.52)	-4.1 (± 22.87)		
Dyspnoea, 15 M, FU, n=95, 60|	-2.5 (± 20.77)	-2.2 (± 26.66)		
Dyspnoea, 18 M, FU, n=90, 59|	-3.0 (± 24.81)	-2.8 (± 29.22)		
Dyspnoea, 21 M, FU, n=87, 52|	-3.4 (± 24.92)	-1.9 (± 21.30)		
Dyspnoea, 24 M, FU, n=69, 49|	-2.4 (± 26.39)	-4.8 (± 24.53)		
Emotional Functioning Cycle 4 Day 1, n=142, 125|	4.4 (± 17.91)	5.4 (± 19.59)		
Emotional Functioning, 1 M, FU, n=139, 122|	5.4 (± 20.26)	7.2 (± 24.08)		
Emotional Functioning, 3 M, FU, n=145, 109|	5.7 (± 20.93)	7.8 (± 20.90)		
Emotional Functioning, 6 M, FU, n=126, 99|	4.8 (± 22.57)	8.9 (± 22.34)		
Emotional Functioning, 9 M, FU, n=115, 85|	3.4 (± 22.95)	6.7 (± 18.52)		
Emotional Functioning. 12 M, FU, n=110, 76|	3.9 (± 22.11)	8.0 (± 21.92)		
Emotional Functioning, 15 M, FU, n=98, 62|	5.1 (± 21.54)	6.5 (± 21.15)		
Emotional Functioning, 18 M, FU, n=90, 61|	5.1 (± 22.94)	6.5 (± 26.35)		
Emotional Functioning, 21 M, FU, n=88, 52|	5.3 (± 22.43)	7.7 (± 23.56)		
Emotional Functioning, 24 M, FU, n=70, 50|	7.1 (± 23.02)	7.1 (± 26.16)		
Fatigue Cycle 4 Day 1, n=142, 126|	-4.3 (± 21.37)	-6.3 (± 22.66)		
Fatigue, 1 M, FU, n=138, 122|	-7.4 (± 25.16)	-4.5 (± 28.64)		

Fatigue, 3 M, FU, n=145, 109|	-5.4 (± 24.01)	-9.3 (± 27.83)		
Fatigue, 6 M, FU, n=126, 99|	-8.2 (± 23.64)	-12.2 (± 22.43)		
Fatigue, 9 M, FU, n=115, 86|	-8.8 (± 23.80)	-9.8 (± 24.56)		
Fatigue. 12 M, FU, n=110, 76|	-6.8 (± 25.28)	-10.3 (± 23.44)		
Fatigue, 15 M, FU, n=97, 76|	-7.6 (± 19.83)	-8.9 (± 27.61)		
Fatigue, 18 M, FU, n=90, 62|	-7.0 (± 22.25)	-6.1 (± 30.15)		
Fatigue, 21 M, FU, n=88, 53|	-9.6 (± 20.44)	-9.1 (± 25.34)		
Fatigue, 24 M, FU, n=70, 50|	-9.1 (± 23.01)	-11.7 (± 25.30)		
Financial Difficulties Cycle 4 Day 1, n=141, 126|	-4.5 (± 23.98)	-6.1 (± 29.93)		
Financial Difficulties, 1 M, FU, n=136, 122|	-5.9 (± 26.57)	-5.2 (± 26.07)		
Financial Difficulties, 3 M, FU, n=145, 108|	-4.1 (± 28.30)	-9.0 (± 29.40)		
Financial Difficulties, 9 M, FU, n=114, 84|	-6.1 (± 27.54)	-8.7 (± 27.44)		
Financial Difficulties. 12 M, FU, n=110, 76|	-6.4 (± 24.93)	-9.6 (± 28.71)		
Financial Difficulties, 15 M, FU, n=96, 62|	-8.3 (± 23.69)	-9.7 (± 27.91)		
Financial Difficulties, 18 M, FU, n=90, 60|	-4.1 (± 24.39)	-12.2 (± 30.04)		
Financial Difficulties, 21 M, FU, n=88, 51|	-10.6 (± 22.34)	-11.1 (± 28.02)		
Financial Difficulties, 24 M, FU, n=70, 50|	-6.2 (± 24.93)	-12.0 (± 27.57)		
Nausea and Vomiting Cycle 4 Day 1, n=142, 126|	2.0 (± 16.06)	3.7 (± 18.37)		
Nausea and Vomiting, 1 M, FU, n=139, 122|	1.0 (± 14.85)	0.1 (± 19.22)		
Nausea and Vomiting, 3 M, FU, n=145, 109|	0.1 (± 15.90)	-2.9 (± 14.49)		
Nausea and Vomiting, 6 M, FU, n=126, 99|	-2.8 (± 13.12)	-2.5 (± 14.36)		
Nausea and Vomiting, 9 M, FU, n=115, 86|	-1.3 (± 13.81)	-1.2 (± 15.08)		
Nausea and Vomiting. 12 M, FU, n=110, 76|	-2.9 (± 13.52)	-1.8 (± 12.35)		
Nausea and Vomiting, 15 M, FU, n=97, 62|	-3.3 (± 11.45)	-2.7 (± 11.76)		
Nausea and Vomiting, 18 M, FU, n=90, 61|	-3.3 (± 12.03)	-2.5 (± 10.02)		
Nausea and Vomiting, 21 M, FU, n=88, 53|	-4.0 (± 13.37)	1.3 (± 11.72)		
Nausea and Vomiting, 24 M, FU, n=70, 50|	-2.4 (± 13.69)	-0.3 (± 11.90)		
Pain Cycle 4 Day 1, n=142, 126|	-3.6 (± 20.64)	-4.2 (± 20.43)		
Pain, 1 M, FU, n=139, 122|	-2.8 (± 23.02)	-5.5 (± 22.31)		
Pain, 3 M, FU, n=145, 109|	-3.8 (± 25.13)	-2.1 (± 24.44)		
Pain, 6 M, FU, n=126, 99|	-5.3 (± 23.54)	-6.6 (± 20.59)		
Pain, 9 M, FU, n=115, 86|	-4.2 (± 23.86)	-4.8 (± 22.12)		
Pain. 12 M, FU, n=110, 76|	-3.5 (± 24.43)	-3.7 (± 21.01)		
Pain, 15 M, FU, n=98, 62|	-2.9 (± 23.08)	-3.5 (± 22.00)		
Pain, 18 M, FU, n=90, 61|	-3.3 (± 19.39)	0.5 (± 28.05)		
Pain, 21 M, FU, n=88, 53|	-5.9 (± 19.74)	-0.9 (± 25.82)		
Pain, 24 M, FU, n=70, 50|	-1.7 (± 23.25)	-3.0 (± 24.67)		

Physical Functioning Cycle 4 Day 1, n=141, 124|	1.2 (± 14.50)	0.6 (± 16.81)		
Physical Functioning, 1 M, FU, n=139, 122|	0.4 (± 19.52)	-0.7 (± 21.15)		
Physical Functioning, 3 M, FU, n=142, 108|	0.9 (± 18.66)	0.9 (± 19.68)		
Physical Functioning, 6 M, FU, n=124, 98|	3.2 (± 16.41)	5.7 (± 17.01)		
Physical Functioning, 9 M, FU, n=113, 83|	3.9 (± 17.30)	6.2 (± 17.25)		
Physical Functioning. 12 M, FU, n=109, 73|	2.4 (± 17.98)	3.5 (± 17.52)		
Physical Functioning, 15 M, FU, n=96, 60|	3.8 (± 14.65)	2.7 (± 18.46)		
Physical Functioning, 18 M, FU, n=90, 60|	4.1 (± 16.65)	0.1 (± 22.09)		
Physical Functioning, 21 M, FU, n=88, 52|	4.7 (± 17.14)	2.1 (± 18.88)		
Physical Functioning, 24 M, FU, n=69, 49|	5.3 (± 17.44)	3.7 (± 20.57)		
Global Health Status Cycle 4 Day 1, n=140, 122|	6.4 (± 23.46)	6.8 (± 17.54)		
Global Health Status, 1 M, FU, n=136, 119|	6.5 (± 24.23)	6.9 (± 26.32)		
Global Health Status, 3 M, FU, n=142, 105|	5.0 (± 21.45)	12.3 (± 21.15)		
Global Health Status, 9 M, FU, n=112, 83|	7.6 (± 23.24)	11.7 (± 22.35)		
Global Health Status. 12 M, FU, n=110, 74|	7.6 (± 23.64)	12.2 (± 21.77)		
Global Health Status, 15 M, FU, n=93, 61|	7.6 (± 20.40)	12.7 (± 22.29)		
Global Health Status, 18 M, FU, n= 89, 60|	9.2 (± 23.03)	10.4 (± 27.00)		
Global Health Status, 21 M, FU, n=87, 53|	10.8 (± 20.26)	12.7 (± 21.53)		
Global Health Status, 24 M, FU, n=68, 48|	12.1 (± 24.28)	12.3 (± 24.31)		
Role Functioning Cycle 4 Day 1,n=140, 124|	1.4 (± 23.27)	0.1 (± 24.83)		
Role Functioning, 1 M, FU, n= 138, 120|	-0.1 (± 25.83)	-0.7 (± 27.53)		
Role Functioning, 3 M, FU, n=141, 107|	0.5 (± 25.19)	0.9 (± 28.94)		
Role Functioning, 6 M, FU, n=124, 97|	4.3 (± 25.49)	5.5 (± 26.54)		
Role Functioning, 9 M, FU, n=113, 83|	4.1 (± 26.21)	6.2 (± 25.60)		
Role Functioning. 12 M, FU, n=109, 72|	2.1 (± 26.46)	3.9 (± 24.78)		
Role Functioning, 15 M, FU, n=96, 60|	3.8 (± 24.84)	1.9 (± 25.13)		
Role Functioning, 18 M, FU, n=90, 60|	7.0 (± 24.09)	-0.0 (± 28.95)		
Role Functioning, 21 M, FU, n=88, 51|	5.3 (± 22.82)	2.6 (± 26.74)		
Role Functioning, 24 M, FU, n=69, 49|	5.8 (± 25.54)	3.7 (± 30.10)		
Social Functioning Cycle 4 Day 1, n=142, 126|	3.1 (± 20.30)	-0.9 (± 23.50)		
Social Functioning, 1 M, FU, n=138, 122|	0.4 (± 25.98)	0.8 (± 27.93)		
Social Functioning, 3 M, FU, n=145, 109|	0.8 (± 23.76)	4.3 (± 26.29)		
Social Functioning, 6 M, FU, n= 126, 99|	3.4 (± 22.04)	6.1 (± 26.24)		
Social Functioning, 9 M, FU, n=115, 84|	2.3 (± 21.84)	4.2 (± 25.46)		
Social Functioning. 12 M, FU, n= 110, 76|	3.0 (± 23.04)	3.3 (± 21.95)		
Social Functioning, 15 M, FU, n=96, 62|	6.2 (± 18.30)	1.6 (± 27.61)		

Social Functioning, 18 M, FU, n=90, 61|	6.5 (± 19.78)	2.7 (± 29.69)		
Social Functioning, 21 M, FU, n=88, 52|	6.6 (± 18.83)	4.5 (± 24.72)		
Social Functioning, 24 M, FU, n=70, 50|	7.9 (± 19.60)	7.7 (± 24.56)		
Insomnia Cycle 4 Day 1, n=138, 123|	-3.1 (± 26.07)	-8.7 (± 26.94)		
Insomnia, 1 M, FU, n=135, 120|	-5.9 (± 29.04)	-11.1 (± 27.78)		
Insomnia, 3 M, FU, n=139, 108|	-6.2 (± 29.64)	-13.3 (± 28.07)		
Insomnia, 6 M, FU, n=121, 98|	-5.2 (± 26.18)	-17.0 (± 25.88)		
Insomnia, 9 M, FU, n=112, 81|	-3.0 (± 30.53)	-13.2 (± 31.04)		
Insomnia. 12 M, FU, n=106, 73|	-6.9 (± 25.91)	-10.5 (± 29.33)		
Insomnia, 15 M, FU, n=96, 59|	-5.9 (± 29.02)	-17.5 (± 26.52)		
Insomnia, 18 M, FU, n=89, 59|	-7.5 (± 28.32)	-15.3 (± 28.58)		
Insomnia, 21 M, FU, n=86, 52|	-8.5 (± 25.15)	-10.3 (± 34.64)		
Insomnia, 24 M, FU, n=68, 49|	-1.5 (± 33.30)	-13.6 (± 35.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean of Health Change Questionnaire (HCQ)

End point title	Mean of Health Change Questionnaire (HCQ)

End point description:

The HCQ consists of a single question in which the participant is asked if he/she has experienced any change in his/her health overall since beginning the study. For HCQ, values from 1 to 9 were assigned to the 9 responses in the HCQ questionnaire, ranging from 1 for 'my health is a great deal better' to 9 for 'my health is a great deal worse' since the beginning of the study. Lower scores represent better conditions.

End point type	Secondary

End point timeframe:

Screening, Cycle 3 Day 1, and 1 M and every 3 month post last dose up to 24 month.

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Cycle 4 Day 1, n=139, 124|	2.6 (± 1.62)	2.8 (± 1.59)		
1 M, FU, n=138, 121|	3.0 (± 2.05)	3.2 (± 2.30)		
3 M, FU, n=141, 108|	3.0 (± 2.11)	2.8 (± 1.86)		
6 M, FU, n=124, 98|	2.6 (± 1.76)	2.6 (± 1.82)		

9 M, FU, n=112, 85|	2.5 (± 1.78)	2.4 (± 1.57)		
12 M, FU, n=108, 74|	2.5 (± 1.80)	2.5 (± 1.78)		
15 M, FU, n=96, 61|	2.2 (± 1.57)	2.3 (± 1.68)		
18 M, FU, n=88, 58|	2.4 (± 1.67)	2.7 (± 2.01)		
21 M, FU, n= 87, 52|	2.3 (± 1.50)	2.3 (± 1.52)		
24 M, FU, n=69, 49|	2.3 (± 1.76)	2.6 (± 1.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean area under the time-concentration curve (AUC) curve over the dosing interval (AUC[0-tau]) of ofatumumab

End point title	Mean area under the time-concentration curve (AUC) curve over the dosing interval (AUC[0-tau]) of ofatumumab[1]

End point description:

Area under the time-concentration curve (AUC) over the dosing interval (AUC[0-tau]) was evaluated. Blood samples were collected from participants who received ofatumumab plus fludarabine and cyclophosphamide predose and 0.5 h after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, predose samples were collected prior to ofatumumab administration at Cycles 2, 3, 5, and 6 (Days 29, 57, 113, and 141).

End point type	Secondary

End point timeframe:

Cycle 1 Week 1, Cycle 1 Week 2, Cycles 2,3,4,5,6

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: descriptive statistics

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: hour*nanogram/mililiter (h*ng/mL)				
geometric mean (confidence interval 95%)				
cycle 1, week 1, n=158|	3554.910 (3224.844 to 3918.759)			
cycle 1, week 2, n=129|	34109.67 (30042.08 to 38728.00)			
cycle 2, n=147|	67069.79 (59485.45 to 75621.13)			
cycle 3, n=129|	84620.05 (76209.86 to 93958.35)			
cycle 4, 107|	89091.35 (78326.34 to 101335.9)			

cycle 5, n=97|	96829.23 (84488.81 to 110972.1)			
cycle 6, n=91|	104798.0 (90904.74 to 120814.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration (Cmax) and observed drug concentration prior to the next dose (Ctrough) of Ofatumumab

End point title	Maximum concentration (Cmax) and observed drug concentration prior to the next dose (Ctrough) of Ofatumumab[2]

End point description:

Blood samples were collected to assess the plasma concentration of ofatumumab.Cmax and Ctrough were determined. Blood samples were collected from participants who received ofatumumab plus fludarabine and cyclophosphamide predose and 0.5 h after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, predose samples were collected prior to ofatumumab administration at Cycles 2, 3, 5, and 6 (Days 29, 57, 113, and 141).

End point type	Secondary

End point timeframe:

Cycle 1 Week 1, Cycle 1 Week 2, Cycles 2,3,4,5

Notes:

[2] - 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: descriptive statistics

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: Micrograms per milliliter				
geometric mean (confidence interval 95%)				
Cmax cycle 1, week 1, n=154|	61.355 (55.444 to 67.897)			
Cmax cycle 1, week 2, n=159|	241.192 (210.492 to 276.369)			
Cmax cycle 4, n=140|	312.745 (287.708 to 339.961)			
Ctrough cycle 1, week 1, n=167|	3.551 (2.417 to 5.217)			
Ctrough cycle 1, week 2, n=165|	9.496 (6.565 to 13.736)			
Ctrough cycle 2, n=162|	24.281 (17.953 to 32.840)			

Ctrough cycle 3,n=150|	25.632 (18.884 to 34.791)			
Ctrough cycle 4,n=130|	58.640 (44.465 to 77.333)			
Ctrough cycle 5, n=113|	70.398 (55.257 to 89.686)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time of occurrence of Cmax (Tmax) of ofatumumab

End point title	Time of occurrence of Cmax (Tmax) of ofatumumab[3]

End point description:

Blood samples were collected from participants who received ofatumumab plus fludarabine and cyclophosphamide predose and 0.5 h after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4.

End point type	Secondary

End point timeframe:

Cycle 1 Week 1, Cycle 1 Week 2, Cycle 4

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: descriptive statistics

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: Hour				
geometric mean (confidence interval 95%)				
cycle 1, week 1,n=154|	6.106 (5.789 to 6.442)			
cycle 1, week 2, n=159|	5.004 (4.896 to 5.114)			
cycle 4, n=140|	4.878 (4.661 to 5.105)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with drug related infections reported as AEs and SAEs of maximum severity of Grade 3 or Higher

End point title	Number of participants with drug related infections reported as

	AEs and SAEs of maximum severity of Grade 3 or Higher

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Maximum severity grades were evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (1, mild; 2, moderate; 3, severe; 4, life-threatening/disabling; 5, death).

End point type	Secondary

End point timeframe:

From first dose of study medication to 60 days after the last dose of study medication (for an AE), or up to 5 years after the last dose of study drug or until the time of the next anti-CLL therapy (for SAE)

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	178		
Units: Participants				
AE|	19	11		
SAE|	25	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who received no transfusion or at Least one transfusion during the study

End point title	Number of participants who received no transfusion or at Least one transfusion during the study

End point description:

Participants who received no transfusion and at least one transfusion during the study are presented. Participants who took any blood products or blood supportive care product are included.

End point type	Secondary

End point timeframe:

From randomization up to 5 years after last dose of study drug

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	178		
Units: Participants				

At least one transfusion|	125	99		
No transfusions|	56	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with at least one Grade 3/Grade 4 myelosuppression adverse events

End point title	Number of participants with at least one Grade 3/Grade 4 myelosuppression adverse events

End point description:

Participants with at least one Grade 3 or Grade 4 myelosuppression (anemia, neutropenia, and thrombocytopenia) are presented. Myelosuppression is defined as the decrease in the ability of the bone marrow to produce blood cells. AEs were graded according to NCI common terminology criteria for adverse events (CTCAE) grade, version 3.0 (1, mild; 2, moderate; 3, severe; 4, life-threatening/disabling; 5, death).

End point type	Secondary

End point timeframe:

From first dose of study medication to 60 days after the last dose of study medication (for an AE), or up to 5 years after the last dose of study drug or until the time of the next anti-CLL therapy (for SAE)

End point values	Ofatumumab + Fludarabine + Cyclophosphamide_ ITT subjects	Fludarabine + Cyclophosphamide_ ITT subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	178		
Units: Participants	126	118		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit up to approximately 8.5 years.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Ofatumumab + Fludarabine + Cyclophosphamide

Reporting group description:

Ofatumumab + Fludarabine + Cyclophosphamide

Reporting group title	Fludarabine + Cyclophosphamide

Reporting group description:

Fludarabine + Cyclophosphamide

Serious adverse events	Ofatumumab + Fludarabine + Cyclophosphamide	Fludarabine + Cyclophosphamide	
Total subjects affected by serious adverse events			
subjects affected / exposed	108 / 181 (59.67%)	86 / 178 (48.31%)	
number of deaths (all causes)	40	42	
number of deaths resulting from adverse events	11	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	3 / 181 (1.66%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	1 / 1	2 / 2	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder papilloma			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopharyngeal cancer			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Melanoma recurrent			

subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Essential hypertension			

subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic vasculitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertension			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombophlebitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	9 / 181 (4.97%)	5 / 178 (2.81%)	
occurrences causally related to treatment / all	4 / 9	3 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 181 (1.66%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 3	0 / 1	
Oedema peripheral			
subjects affected / exposed	1 / 181 (0.55%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 181 (1.66%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	1 / 2	1 / 1	
Dyspnoea			
subjects affected / exposed	3 / 181 (1.66%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Acute respiratory failure			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial haemorrhage			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary fibrosis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract haemorrhage			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Hip fracture			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Epidermolysis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 181 (1.10%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 181 (1.10%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardiac failure acute			
subjects affected / exposed	0 / 181 (0.00%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Angina pectoris			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			

subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Extrasystoles			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia paroxysmal			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid arteriosclerosis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dementia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (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			
Febrile neutropenia			
subjects affected / exposed	18 / 181 (9.94%)	15 / 178 (8.43%)	
occurrences causally related to treatment / all	15 / 24	12 / 24	
deaths causally related to treatment / all	2 / 2	0 / 0	
Neutropenia			
subjects affected / exposed	17 / 181 (9.39%)	14 / 178 (7.87%)	
occurrences causally related to treatment / all	17 / 21	15 / 18	
deaths causally related to treatment / all	0 / 0	0 / 2	
Anaemia			
subjects affected / exposed	11 / 181 (6.08%)	12 / 178 (6.74%)	
occurrences causally related to treatment / all	2 / 12	12 / 18	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombocytopenia			

subjects affected / exposed	7 / 181 (3.87%)	10 / 178 (5.62%)	
occurrences causally related to treatment / all	3 / 7	7 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancytopenia			
subjects affected / exposed	5 / 181 (2.76%)	5 / 178 (2.81%)	
occurrences causally related to treatment / all	4 / 5	3 / 6	
deaths causally related to treatment / all	1 / 1	0 / 1	
Autoimmune haemolytic anaemia			
subjects affected / exposed	2 / 181 (1.10%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 181 (1.10%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agranulocytosis			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia pure red cell			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulocytopenia			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 181 (1.66%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	2 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 181 (1.66%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Colitis			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary hypersecretion			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 181 (0.55%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			

subjects affected / exposed	5 / 181 (2.76%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (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	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	28 / 181 (15.47%)	29 / 178 (16.29%)	
occurrences causally related to treatment / all	14 / 34	9 / 32	
deaths causally related to treatment / all	1 / 4	3 / 11	

Urinary tract infection			
subjects affected / exposed	6 / 181 (3.31%)	6 / 178 (3.37%)	
occurrences causally related to treatment / all	1 / 11	3 / 7	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	4 / 181 (2.21%)	8 / 178 (4.49%)	
occurrences causally related to treatment / all	1 / 4	1 / 8	
deaths causally related to treatment / all	1 / 4	0 / 4	
Neutropenic sepsis			
subjects affected / exposed	4 / 181 (2.21%)	5 / 178 (2.81%)	
occurrences causally related to treatment / all	3 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 181 (2.21%)	5 / 178 (2.81%)	
occurrences causally related to treatment / all	1 / 4	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	6 / 181 (3.31%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	2 / 6	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 181 (1.66%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 181 (0.55%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cellulitis			
subjects affected / exposed	2 / 181 (1.10%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			

subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 181 (0.55%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 181 (0.55%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cytomegalovirus infection			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	1 / 181 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 181 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter infection			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anal abscess			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial infection			

subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atypical pneumonia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal candidiasis			

subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumocystis jirovecii infection			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia haemophilus			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic mycosis			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B reactivation			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	2 / 181 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Starvation			

subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ofatumumab + Fludarabine + Cyclophosphamide	Fludarabine + Cyclophosphamide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 181 (82.32%)	123 / 178 (69.10%)	
Investigations			
Platelet count decreased			
subjects affected / exposed	12 / 181 (6.63%)	5 / 178 (2.81%)	
occurrences (all)	14	9	
Vascular disorders			
Hypotension			
subjects affected / exposed	11 / 181 (6.08%)	4 / 178 (2.25%)	
occurrences (all)	12	4	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 181 (8.29%)	6 / 178 (3.37%)	
occurrences (all)	18	7	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	38 / 181 (20.99%)	55 / 178 (30.90%)	
occurrences (all)	50	69	
Neutropenia			

subjects affected / exposed	93 / 181 (51.38%)	62 / 178 (34.83%)	
occurrences (all)	192	126	
Leukopenia			
subjects affected / exposed	27 / 181 (14.92%)	10 / 178 (5.62%)	
occurrences (all)	38	29	
Anaemia			
subjects affected / exposed	24 / 181 (13.26%)	38 / 178 (21.35%)	
occurrences (all)	40	51	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	26 / 181 (14.36%)	15 / 178 (8.43%)	
occurrences (all)	40	18	
Asthenia			
subjects affected / exposed	13 / 181 (7.18%)	16 / 178 (8.99%)	
occurrences (all)	15	16	
Fatigue			
subjects affected / exposed	15 / 181 (8.29%)	11 / 178 (6.18%)	
occurrences (all)	19	12	
Chills			
subjects affected / exposed	14 / 181 (7.73%)	3 / 178 (1.69%)	
occurrences (all)	19	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	45 / 181 (24.86%)	36 / 178 (20.22%)	
occurrences (all)	75	73	
Vomiting			
subjects affected / exposed	19 / 181 (10.50%)	22 / 178 (12.36%)	
occurrences (all)	23	28	
Diarrhoea			
subjects affected / exposed	14 / 181 (7.73%)	19 / 178 (10.67%)	
occurrences (all)	17	22	
Constipation			
subjects affected / exposed	8 / 181 (4.42%)	11 / 178 (6.18%)	
occurrences (all)	8	11	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	15 / 181 (8.29%)	10 / 178 (5.62%)	
occurrences (all)	20	12	
Dyspnoea			
subjects affected / exposed	15 / 181 (8.29%)	3 / 178 (1.69%)	
occurrences (all)	22	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	23 / 181 (12.71%)	8 / 178 (4.49%)	
occurrences (all)	30	11	
Pruritus			
subjects affected / exposed	19 / 181 (10.50%)	2 / 178 (1.12%)	
occurrences (all)	23	2	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 181 (7.18%)	8 / 178 (4.49%)	
occurrences (all)	15	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 181 (7.18%)	8 / 178 (4.49%)	
occurrences (all)	14	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2014	Study Name and Logo added. Name of Physician Study Leader updated. Investigator Agreement Page updated. SAEs no longer reported after commencement of subsequent anti-CLL therapy. Prohibited concomitant medication, Glucocorticoid dosing amended. Requirement to collect anticancer and anti-infectious concomitant medications after 1 month follow-up amended to collect only if associated with an SAE and only until subsequent anti-CLL therapy is initiated. Details regarding reporting of study results to investigators, to a publically available register, and for publication updated. Investigator responsibilities with regard to Quality Compliance and Quality Assurance updated. Minor clarifications and typographical errors addressed.
30 September 2014	Clinical Investigational Leader and associated contact information updated. Introduction updated with current published data. Statistical assumptions for event rate projection updated.
20 February 2015	Name of Physician Project Lead and Sponsor Signatory updated. The requirement to report SAEs after commencement of subsequent anti-CLL therapy has been reinstated in India only, to comply with changed country-specific requirements.
08 March 2016	Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Make administrative changes to align with Novartis processes and procedures.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: