Clinical trial results:
A Multicentric, Open-Label, Single Arm Study of Obinutuzumab Short Duration Infusion (SDI) in Patients with Previously Untreated Advanced Follicular Lymphoma

Summary

EudraCT number	2018-003255-38
Trial protocol	NL DE
Global end of trial date	25 January 2023

Results information

Result version number	v3
This version publication date	02 February 2024
First version publication date	04 August 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MO40597

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03817853
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This open-label, single arm study evaluated the safety of obinutuzumab administered as a short duration infusion (SDI; target 90-minute infusion) during cycle 2 and from cycle 2 onwards in combination with chemotherapy in participants with previously untreated advanced follicular lymphoma (FL).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 February 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Brazil: 19
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	113
EEA total number of subjects	45

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)	69
From 65 to 84 years	43
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 35 sites across 7 countries.

Pre-assignment

Screening details:

Of the all participants population (114 participants), one participant did not receive the study treatment, thus the safety-evaluable population included 113 participants.

Period 1

Period 1 title	Induction Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Participants

Arm description:

Participants were enrolled in an induction phase and received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

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

Dosage and administration details:

During induction, obinutuzumab was administered as a 1000 mg IV infusion on Day 1, 8 and 15 during Cycle 1, and on Day 1 of subsequent cycles, for 6-8 cycles. Each cycle is 21 or 28 days long depending on the chemotherapy regimen allocated.

During maintenance, 1000 mg of obinutuzumab as single agent was administered as an SDI every 8 weeks (+ or - 10 days) for 2 years or until disease progression).

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

Dosage and administration details:

Bendamustine was administered on Days 1 and 2 for Cycles 1–6 at a dose of 90 mg/m2/day, for six 28-day cycles.

Investigational medicinal product name	Prednisone/Prednisolone/Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 100 mg (or equivalent prednisolone or methylprednisolone), administered orally on Days 1-5 of each 21-day cycle, for six cycles for CHOP treatment or eight cycles for CVP treatment.

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

Dosage and administration details:

Doxorubicin 50 mg/m^2 IV, administered on Day 1 of each 21-day cycle, for six cycles.

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

Dosage and administration details:

Vincristine 1.4 mg/m^2 (maximum 2 mg) IV, administered on Day 1 of each 21-day cycle, for six cycles for CHOP treatment or eight cycles for CVP treatment.

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

Dosage and administration details:

Cyclophosphamide 750 milligrams per square metre (mg/m^2), administered intravenously (IV) on Day 1 of each 21-day cycle, for six cycles for CHOP treatment or eight cycles for CVP treatment.

Number of subjects in period 1	All Participants
Started	113
Started Maintenance	95
Completed Maintenance	67 [1]
Started Follow-up	99
Completed Follow-up	92 [2]
Completed	93
Not completed	20
Physician decision	2
Consent withdrawn by subject	4
Adverse Event	5
Progressive Disease	6
Various reasons	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: As this is a single arm study, we are displaying the numbers of those who continued on in the study through maintenance and follow-up.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.

Justification: As this is a single arm study, we are displaying the numbers of those who continued on in the study through maintenance and follow-up.

Baseline characteristics

Reporting groups	
Reporting group title	All Participants

Reporting group description:

Participants were enrolled in an induction phase and received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

Reporting group values	All Participants	Total	
Number of subjects	113	113	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	69	69	
From 65-84 years	43	43	
85 years and over	1	1	
Age Continuous Units: years			
arithmetic mean	58.9		
standard deviation	± 12.7	-	
Sex: Female, Male Units: Subjects			
Male	57	57	
Female	56	56	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	33	33	
Not Hispanic or Latino	80	80	
Race (NIH/OMB) Units: Subjects			
Asian	27	27	
White	82	82	
Other	2	2	
Multiple	2	2	

End points

End points reporting groups

Reporting group title	All Participants

Reporting group description:

Participants were enrolled in an induction phase and received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

Subject analysis set title	Short duration infusion population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This population included all enrolled participants who did not experience a Grade 3 or 4 IRR during Cycle 1 (i.e. at any of the 3 Cycle 1 infusions) and received obinutuzumab as an SDI at Cycle 2.

Subject analysis set title	Maintenance: Obinutuzumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

Participants who achieved a partial response (PR) or complete response (CR) following the induction phase received obinutuzumab maintenance therapy. 1000 mg of obinutuzumab as single agent was administered as an SDI every 8 weeks (+ or - 10 days) for 2 years or until disease progression).

Subject analysis set title	Follow-up
Subject analysis set type	Per protocol

Subject analysis set description:

Participants with stable disease (SD) or progressive disease (PD) as best response after induction therapy discontinued study treatment and underwent a safety follow-up visit at 3 months (90 days (+ or - 10 days)). All participants were followed up at 3 months (90 days (+ or - 10 days)) from the time of the last dose of study treatment.

Primary: Percentage of Grade >=3 Infusion-Related Reactions (IRRs) During Cycle 2 in Patients Who Had Previously Received Obinutuzumab at the Standard Infusion Rate During Cycle 1 Without Experiencing a Grade 3 or 4 IRR

End point title	Percentage of Grade >=3 Infusion-Related Reactions (IRRs) During Cycle 2 in Patients Who Had Previously Received Obinutuzumab at the Standard Infusion Rate During Cycle 1 Without Experiencing a Grade 3 or 4 IRR[1]

End point description:

IRRs were defined as all adverse events (AEs) that occurred during or within 24 hours from the end of study treatment infusion and were judged as related to infusion of study treatment components by the investigator. The Short Duration Infusion (SDI) population included all enrolled particpants who did not experience a Grade 3 or 4 IRR during cycle 1 (i.e. at any of the three Cycle 1 infusions), received obinutuzumab given at the standard rate only during Cycle 1, and received obinutuzumab as an SDI at cycle 2.

End point type	Primary

End point timeframe:

Within 24 hours from the end of study treatment infusion of Day 1 in Cycle 2 (1 cycle: 21 or 28 days depending on the chemotherapy selected)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint is presented with a point estimate and a 95% confidence interval according to Clopper&Pearson

End point values	Short duration infusion population			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: Percentage of Participants				
number (confidence interval 95%)	0 (0.00 to 3.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of IRRs Regardless of Grade by Cycle

End point title	Percentage of IRRs Regardless of Grade by Cycle

End point description:

IRRs were defined as all adverse events (AEs) that occurred during or within 24 hours from the end of study treatment infusion and were judged as related to infusion of study treatment components by the investigator. The safety population included all participants who received at least one dose of obinutuzumab.

End point type	Secondary

End point timeframe:

Within 24 hours from the end of study treatment infusion in all cycles, including maintenance ((1 cycle: 21 or 28 days depending on the chemotherapy selected); up to approximately 2.5 years)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Percentage of Participants				
number (not applicable)				
Cycle 1 Day 1 (n=113)	50.4			
Cycle 1 Day 2 (n=51)	7.8			
Cycle 1 Day 8 (n=112)	5.4			
Cycle 1 Day 15 (n=111)	4.5			
Cycle 2 (n=110)	11.8			
Cycle 3 (n=108)	8.3			
Cycle 4 (n=108)	6.5			
Cycle 5 (n=107)	5.6			
Cycle 6 (n=105)	4.8			
Cycle 7 (n=55)	3.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs)

End point title	Percentage of Participants With Adverse Events (AEs)

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant who was administered a pharmaceutical product, regardless of causal attribution. An AE was therefore any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Pre-existing conditions which worsened during the study, recurrence of an intermittent medical condition, deterioration in a laboratory value or other clinical test or were related to a protocol-mandated intervention were also considered AEs. Grading was completed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. The safety population included all participants who received at least one dose of obinutuzumab.

End point type	Secondary

End point timeframe:

Baseline up to end of study (approximately 4 years)

End point values	All Participants	Maintenance: Obinutuzumab	Follow-up	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	113	95	99	
Units: Percentage of Participants				
number (not applicable)	99.1	90.5	27.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to IRR From Infusion to Onset of the IRR During Cycle 2

End point title	Time to IRR From Infusion to Onset of the IRR During Cycle 2

End point description:

Time to IRR (of any grade) in Cycle 2 was defined as the time from the start of infusion (i.e., start date/time of infusion of the first component of study treatment) in Cycle 2 to the onset of the IRR (of any grade) during Cycle 2. The SDI population included all enrolled particpants who did not experience a Grade 3 or 4 IRR during cycle 1 (i.e. at any of the three Cycle 1 infusions), received obinutuzumab given at the standard rate only during Cycle 1, and received obinutuzumab as an SDI at cycle 2. For this outcome measure, only one participant was analyzed. 9999999 = Standard deviation (SD) is not available because only 1 participant had the time to IRR recorded and the SD for one value is not defined.

End point type	Secondary

End point timeframe:

From infusion to onset of IRR during Cycle 2 (1 cycle: 21 or 28 days depending on the chemotherapy selected)

End point values	Short duration infusion population			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Hours				
arithmetic mean (standard deviation)	11.800 (± 9999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration (In Minutes) of Obinutuzumab Administration by Cycle

End point title	Duration (In Minutes) of Obinutuzumab Administration by Cycle

End point description:

The duration of obinutuzumab administration (in minutes) by cycle was defined as the difference between the end time and the start time of obinutuzumab administration. The safety population included all participants who received at least one dose of obinutuzumab.

End point type	Secondary

End point timeframe:

All cycles including maintenance (1 cycle: 21 or 28 days depending on the chemotherapy selected; up to approximately 2.5 years)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Minutes				
arithmetic mean (standard deviation)				
Cycle(C) 1 Day(D) 1 (n=100)	295.96 (± 147.87)			
C1D8 (n=107)	215.97 (± 46.99)			
C1D15 (n=102)	208.91 (± 33.13)			
C2 (n=103)	101.48 (± 20.56)			
C3 (n=101)	103.29 (± 65.45)			
C4 (n=101)	99.26 (± 13.90)			
C5 (n=100)	98.46 (± 16.48)			

C6 (n=102)	99.10 (± 12.18)			
C7 (n=51)	98.84 (± 13.61)			
C8 (n=50)	95.68 (± 4.12)			
Maintenance Week 1 (n=83)	97.64 (± 10.08)			
Maintenance Week 9 (n=63)	96.78 (± 8.49)			
Maintenance Week 17 (n=48)	97.77 (± 7.66)			
Maintenance Week 25 (n=31)	97.16 (± 7.23)			
Maintenance Week 33 (n=24)	95.08 (± 4.27)			
Maintenance Week 41 (n=13)	95.77 (± 5.26)			
Maintenance Week 49 (n=9)	93.56 (± 4.48)			
Maintenance Week 57 (n=2)	93.50 (± 4.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Grade >=3 IRRs Associated with the obinutuzumab Administered as an SDI by Cycle

End point title	Duration of Grade >=3 IRRs Associated with the obinutuzumab Administered as an SDI by Cycle

End point description:

The duration, in minutes, of IRRs during all cycles, where obinutuzumab was administered as an SDI. The safety population included all participants who received at least one dose of obinutuzumab. For this outcome measure, only one participant was analyzed.

End point type	Secondary

End point timeframe:

All cycles including maintenance (1 cycle: 21 or 28 days depending on the chemotherapy selected; up to approximately 2.5 years)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Minutes				
arithmetic mean (standard deviation)				
Cycle 5	()			

Notes:

[2] - No data reported

Statistical analyses

No statistical analyses for this end point

Secondary: Type of Grade >=3 IRRs Associated with the obinutuzumab Administered as an SDI by Cycle

End point title	Type of Grade >=3 IRRs Associated with the obinutuzumab

	Administered as an SDI by Cycle

End point description:

The safety population included all participants who received at least one dose of obinutuzumab. Only 1 participant had a Grade >=3 IRR, with 3 symptoms in Cycle 5. Weight increased was a grade 1 symptom belonging to the grade 3 IRRs.

End point type	Secondary

End point timeframe:

All cycles including maintenance (1 cycle: 21 or 28 days depending on the chemotherapy selected; up to approximately 2.5 years)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of Participants				
number (not applicable)				
Cycle (C) 5- Hypertension (n=1)	33.3			
C5 - Renal failure (n=1)	33.3			
C5 - Weight increased (n=1)	33.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) at the End of Induction (EOI) Therapy

End point title	Objective Response Rate (ORR) at the End of Induction (EOI) Therapy

End point description:

ORR at EOI therapy was defined as the percentage of particpants with either a CR, CR unconfirmed or PR at the EOI visit, as determined by the investigator and according to the guidelines used at the site. The safety population included all participants who received at least one dose of obinutuzumab.

End point type	Secondary

End point timeframe:

Baseline up to end of induction therapy (up to approximately 6 months)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Percentage of Participants				
number (not applicable)				
Complete Response (n=77)	68.1			
Complete Response unconfirmed (n=0)	0			
Partial Response (n=22)	19.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at the End of the Study

End point title	Overall Survival (OS) at the End of the Study

End point description:

OS was defined as the time from start of treatment (date of first intake of any study treatment component) to death from any cause. The safety population included all participants who received at least one dose of obinutuzumab. 9999999 = Due to low number of events, the median and upper CI limit was not evaluable.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to approximately 4 years)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Months				
median (confidence interval 95%)	9999999 (33.97 to 9999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Rate at the End of the Study

End point title	Progression-Free Survival (PFS) Rate at the End of the Study

End point description:

PFS was defined as the time from start of treatment to the first occurrence of disease progression as assessed by the investigator according to the guidelines used at the site or death from any cause. The safety population included all participants who received at least one dose of obinutuzumab. 9999999 = Due to the low number of events, the upper CI limit was not evaluable.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to approximately 4 years)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Months				
median (confidence interval 95%)	33.97 (32.13 to 9999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) Rate at 30 Months (CR30), as Assessed by the Investigator and According to the Guidelines Used at the Site

End point title	Complete Response (CR) Rate at 30 Months (CR30), as Assessed by the Investigator and According to the Guidelines Used at the Site

End point description:

The CR30 rate was defined as the percentage of participants with a CR at 30 months from study treatment initiation (date of first intake of any study treatment component), as determined by the investigator according to the guidelines used at the site. The safety population included all participants who received at least one dose of obinutuzumab.

End point type	Secondary

End point timeframe:

Baseline up to 30 months

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Percentage of Participants				
number (confidence interval 95%)	55.6 (45.68 to 65.12)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (approximately 4 years)

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant who was administered a pharmaceutical product, regardless of causal attribution. Grading was completed according to the CTCAE, version 5.0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	All Participants

Reporting group description:

Participants were enrolled in an induction phase and received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

Reporting group title	Follow-up

Reporting group description:

Participants with stable disease (SD) or progressive disease (PD) as best response after induction therapy discontinued study treatment and underwent a safety follow-up visit at 3 months (90 days (+ or - 10 days)). All participants were followed up at 3 months (90 days (+ or - 10 days)) from the time of the last dose of study treatment.

Reporting group title	Maintenance

Reporting group description:

Participants who achieved a partial response (PR) or complete response (CR) following the induction phase received obinutuzumab maintenance therapy. 1000 mg of obinutuzumab as single agent was administered as an SDI every 8 weeks (+ or - 10 days) for 2 years or until disease progression).

Serious adverse events	All Participants	Follow-up	Maintenance
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 113 (18.58%)	11 / 99 (11.11%)	17 / 95 (17.89%)
number of deaths (all causes)	9	4	8
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic bronchial carcinoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			

subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 113 (0.00%)	1 / 99 (1.01%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obliterative bronchiolitis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 113 (0.00%)	1 / 99 (1.01%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 99 (1.01%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiorenal syndrome			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 113 (1.77%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	5 / 113 (4.42%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 113 (0.00%)	1 / 99 (1.01%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia streptococcal			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 113 (2.65%)	1 / 99 (1.01%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster disseminated			
subjects affected / exposed	0 / 113 (0.00%)	1 / 99 (1.01%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 113 (0.88%)	4 / 99 (4.04%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 1	0 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			

subjects affected / exposed	0 / 113 (0.00%)	1 / 99 (1.01%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Severe acute respiratory syndrome			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary sepsis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 113 (0.00%)	3 / 99 (3.03%)	4 / 95 (4.21%)
occurrences causally related to treatment / all	0 / 0	0 / 3	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 3
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 99 (1.01%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			

subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	All Participants	Follow-up	Maintenance
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 113 (98.23%)	13 / 99 (13.13%)	76 / 95 (80.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 113 (4.42%)	0 / 99 (0.00%)	7 / 95 (7.37%)
occurrences (all)	5	0	8
Hypotension			
subjects affected / exposed	7 / 113 (6.19%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences (all)	8	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 113 (13.27%)	0 / 99 (0.00%)	11 / 95 (11.58%)
occurrences (all)	18	0	14
Mucosal inflammation			
subjects affected / exposed	9 / 113 (7.96%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences (all)	9	0	0
Malaise			
subjects affected / exposed	12 / 113 (10.62%)	0 / 99 (0.00%)	2 / 95 (2.11%)
occurrences (all)	15	0	2
Fatigue			
subjects affected / exposed	18 / 113 (15.93%)	1 / 99 (1.01%)	3 / 95 (3.16%)
occurrences (all)	19	1	3
Asthenia			

subjects affected / exposed	11 / 113 (9.73%)	1 / 99 (1.01%)	6 / 95 (6.32%)
occurrences (all)	13	1	6
Oedema peripheral			
subjects affected / exposed	4 / 113 (3.54%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	4	0	4
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 113 (2.65%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	3	0	5
Cough			
subjects affected / exposed	10 / 113 (8.85%)	0 / 99 (0.00%)	12 / 95 (12.63%)
occurrences (all)	10	0	13
Hiccups			
subjects affected / exposed	6 / 113 (5.31%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences (all)	8	0	0
Oropharyngeal pain			
subjects affected / exposed	5 / 113 (4.42%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	5	0	4
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 113 (16.81%)	1 / 99 (1.01%)	5 / 95 (5.26%)
occurrences (all)	19	1	5
Anxiety			
subjects affected / exposed	6 / 113 (5.31%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences (all)	6	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 113 (8.85%)	1 / 99 (1.01%)	4 / 95 (4.21%)
occurrences (all)	14	1	4
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 113 (6.19%)	1 / 99 (1.01%)	3 / 95 (3.16%)
occurrences (all)	10	1	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 113 (2.65%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	3	0	4

Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	69 / 113 (61.06%)	0 / 99 (0.00%)	3 / 95 (3.16%)
occurrences (all)	128	0	3
Fall			
subjects affected / exposed	4 / 113 (3.54%)	0 / 99 (0.00%)	3 / 95 (3.16%)
occurrences (all)	4	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 113 (6.19%)	0 / 99 (0.00%)	3 / 95 (3.16%)
occurrences (all)	7	0	3
Headache			
subjects affected / exposed	18 / 113 (15.93%)	0 / 99 (0.00%)	7 / 95 (7.37%)
occurrences (all)	19	0	7
Neuropathy peripheral			
subjects affected / exposed	19 / 113 (16.81%)	0 / 99 (0.00%)	3 / 95 (3.16%)
occurrences (all)	19	0	3
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 113 (7.96%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences (all)	13	0	1
Paraesthesia			
subjects affected / exposed	5 / 113 (4.42%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences (all)	5	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 113 (17.70%)	1 / 99 (1.01%)	3 / 95 (3.16%)
occurrences (all)	25	1	3
Neutropenia			
subjects affected / exposed	68 / 113 (60.18%)	2 / 99 (2.02%)	16 / 95 (16.84%)
occurrences (all)	116	2	27
Lymphopenia			
subjects affected / exposed	22 / 113 (19.47%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	36	0	5
Leukopenia			
subjects affected / exposed	20 / 113 (17.70%)	0 / 99 (0.00%)	3 / 95 (3.16%)
occurrences (all)	34	0	6

Thrombocytopenia			
subjects affected / exposed	20 / 113 (17.70%)	1 / 99 (1.01%)	4 / 95 (4.21%)
occurrences (all)	28	1	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 113 (13.27%)	1 / 99 (1.01%)	5 / 95 (5.26%)
occurrences (all)	18	1	6
Constipation			
subjects affected / exposed	39 / 113 (34.51%)	0 / 99 (0.00%)	6 / 95 (6.32%)
occurrences (all)	42	0	6
Abdominal pain upper			
subjects affected / exposed	9 / 113 (7.96%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	10	0	4
Abdominal pain			
subjects affected / exposed	11 / 113 (9.73%)	1 / 99 (1.01%)	3 / 95 (3.16%)
occurrences (all)	13	1	3
Vomiting			
subjects affected / exposed	15 / 113 (13.27%)	0 / 99 (0.00%)	1 / 95 (1.05%)
occurrences (all)	17	0	1
Nausea			
subjects affected / exposed	48 / 113 (42.48%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	67	0	6
Dyspepsia			
subjects affected / exposed	8 / 113 (7.08%)	0 / 99 (0.00%)	3 / 95 (3.16%)
occurrences (all)	8	0	4
Stomatitis			
subjects affected / exposed	5 / 113 (4.42%)	0 / 99 (0.00%)	3 / 95 (3.16%)
occurrences (all)	5	0	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	17 / 113 (15.04%)	1 / 99 (1.01%)	1 / 95 (1.05%)
occurrences (all)	18	1	1
Rash maculo-papular			
subjects affected / exposed	6 / 113 (5.31%)	0 / 99 (0.00%)	0 / 95 (0.00%)
occurrences (all)	7	0	0
Night sweats			

subjects affected / exposed	0 / 113 (0.00%)	0 / 99 (0.00%)	5 / 95 (5.26%)
occurrences (all)	0	0	5
Dry skin			
subjects affected / exposed	3 / 113 (2.65%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	3	0	5
Pruritus			
subjects affected / exposed	5 / 113 (4.42%)	0 / 99 (0.00%)	2 / 95 (2.11%)
occurrences (all)	5	0	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	14 / 113 (12.39%)	0 / 99 (0.00%)	8 / 95 (8.42%)
occurrences (all)	16	0	9
Bone pain			
subjects affected / exposed	11 / 113 (9.73%)	0 / 99 (0.00%)	2 / 95 (2.11%)
occurrences (all)	14	0	2
Arthralgia			
subjects affected / exposed	7 / 113 (6.19%)	0 / 99 (0.00%)	13 / 95 (13.68%)
occurrences (all)	7	0	14
Pain in extremity			
subjects affected / exposed	3 / 113 (2.65%)	0 / 99 (0.00%)	4 / 95 (4.21%)
occurrences (all)	3	0	4
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 113 (2.65%)	1 / 99 (1.01%)	6 / 95 (6.32%)
occurrences (all)	3	1	7
Upper respiratory tract infection			
subjects affected / exposed	7 / 113 (6.19%)	1 / 99 (1.01%)	2 / 95 (2.11%)
occurrences (all)	7	1	3
COVID-19			
subjects affected / exposed	0 / 113 (0.00%)	5 / 99 (5.05%)	11 / 95 (11.58%)
occurrences (all)	0	5	12
Herpes zoster			
subjects affected / exposed	4 / 113 (3.54%)	0 / 99 (0.00%)	2 / 95 (2.11%)
occurrences (all)	4	0	2
Nasopharyngitis			

subjects affected / exposed	4 / 113 (3.54%)	0 / 99 (0.00%)	6 / 95 (6.32%)
occurrences (all)	4	0	6
Sinusitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 99 (0.00%)	6 / 95 (6.32%)
occurrences (all)	1	0	7
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 113 (6.19%)	0 / 99 (0.00%)	3 / 95 (3.16%)
occurrences (all)	7	0	3
Hyperuricaemia			
subjects affected / exposed	7 / 113 (6.19%)	0 / 99 (0.00%)	5 / 95 (5.26%)
occurrences (all)	7	0	6
Hypokalaemia			
subjects affected / exposed	5 / 113 (4.42%)	1 / 99 (1.01%)	1 / 95 (1.05%)
occurrences (all)	5	1	1
Vitamin D deficiency			
subjects affected / exposed	2 / 113 (1.77%)	0 / 99 (0.00%)	8 / 95 (8.42%)
occurrences (all)	2	0	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2018	This amendment was created to clarify that participants with prior radiotherapy for FL were excluded from the study; clarification that rescreening of participants was possible at any time; the guidance on the use of premedication before obinutuzumab infusion to reduce the risk of IRRs in participants was updated; additional guidance was provided on hepatitis B reactiviation management; clarification was added that the assessment of LVEF was only required for participants who received obinutuzumab with CHOP chemotherapy; assessments of B symptoms at the end-of-infusion, during maintenance, and at the end-of maintenance was not required and that it was only mandatory at screening; clarifications were added to state the assessments of weight at follow-up and response assessments at screening were not required; clarification that hepatitis B virus DNA PCR testing would be performed every 3-4 weeks for participants with prior HBV infection of who are carriers of HBV; the study title was updated to change “Gazyva” to “obinutuzumab” since the trade name differs depending on the country.
06 December 2018	This protocol was amended to state that the addition to the steroid premedication, participants would also receive premedication with an anti-histamine and antipyretic before the first cycle of obinutuzumab given as an SDI.
12 September 2019	The protocol was amended to allow participants who experienced a first Grade 3 IRR during SDI dosing to continue to receive SDI dosing during their current and next infusion. The statistical analysis plan was updated to include earlier reporting of the efficacy data at the EOI therapy. Clarification that the SDI population was used for the analysis of the secondary safety endpoint and the primary endpoint analysis. Exclusion criteria was updated to exclude participants with known HTLV-1 infection. Updates to the inclusion criteria allowed participants treated with corticosteroids for reasons other than chemotherapy and premedication to reduce the risk of IRRs as long as the dose didn't exceed 30 mg/day and to clarify that the frequency and period of DNA testing in participants with occult or prior HBV infection and with undetectable HBV DNA would be at least every 3 months for willing participants. The secondary safety endpoint was revised to clarify that it included IRRs linked to any study treatment. The following was clarified: participants who began a prohibited therapy would discontinue the study treatment and the end of induction or end of maintenance visit was performed before any new therapy was started, that 'study treatment' referred to obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance, that Beta-2 microglobulin testing would be conducted at screening and EOI, the infusion rates at which obinutuzumab would be restarted following IRRs; premedication that would be given for IRRs, participants with a Grade 4 IRR during induction would discontinue study treatment (and not discontinue the study). This amendment also included additional guidance on when maintenance therapy began, managing suspected anaphylactic reactions, how often to assess vital signs, on tumor and bone marrow assessments and how participant and provided-reported outcome instruments would be administered, the timing of assessments and follow-up period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported