



Clinical trial results:

Rituximab with or without Ibrutinib for untreated patients with advanced follicular lymphoma in need of therapy.

Summary

EudraCT number	2015-001487-19
Trial protocol	NO DK SE FI AT
Global end of trial date	15 July 2023

Results information

Result version number	v1 (current)
This version publication date	05 October 2024
First version publication date	05 October 2024

Trial information

Trial identification

Sponsor protocol code	SAKK 35/14
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02451111
WHO universal trial number (UTN)	-
Other trial identifiers	SNCTP No: SNCTP000001327

Notes:

Sponsors

Sponsor organisation name	Swiss Group For Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group For Clinical Cancer Research (SAKK), +41 31389 91 91, sakkcc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group For Clinical Cancer Research (SAKK), +41 31389 91 91, sakkcc@sakk.ch

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	17 June 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 July 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to study the activity and the safety of the 1st line treatment with Ibrutinib in combination with Rituximab for patients with advanced follicular lymphoma in need of therapy.

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continuous assessment of laboratory values and vital signs.

Background therapy:

Not applicable.

Evidence for comparator:

For symptomatic follicular lymphoma (fl) patients with more advanced tumor burden, in need of initial treatment, the combination of Rituximab and chemotherapy, possibly followed by Rituximab maintenance became a new standard in many countries [PMID: 23433739, PMID: 21176949].

In a setting of a chemotherapy-free strategy, the clinical study of Rituximab combinations with other immunotherapies or with novel targeted agents is obvious relevant. Promising results have also been reported with the combination of Rituximab and lenalidomide.

The combination of Rituximab and Ibrutinib has been tested in clinical trials and appeared to be well tolerated and active [PMID: 25150798]. Since Ibrutinib seems to achieve better results when administered for prolonged time as shown in Chronic Lymphocytic Leukemia (CLL), it was chosen to compare its combination with Rituximab to the prolonged Rituximab-only schedule that was already shown to be very active in the SAKK 35/03 trial [see results for EudraCT No. 2004-002859-13].

Actual start date of recruitment	06 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 28
Country: Number of subjects enrolled	Sweden: 28
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	Switzerland: 104
Worldwide total number of subjects	192
EEA total number of subjects	88

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)	119
From 65 to 84 years	72
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

197 patients at 36 sites in Austria (1 site, 1 patient), Denmark (4 sites, 16 patients), Finland (3 sites, 15 patients), Norway (3 sites, 29 patients), Sweden (5 sites, 28 patients) and Switzerland (20 sites, 108 patients) were registered from 06-Nov-2015 to 22-Jun-2020. Of these, 196 patients were randomized; 192 patients received trial treatment.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fulfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

Pre-assignment period milestones

Number of subjects started	203 ^[1]
Number of subjects completed	196

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 6
Reason: Number of subjects	Not randomized: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number enrolled in the trial reflects patients being enrolled and receiving medication. The number of screened patients is 203, the number of registered patients is 197, the number of randomized patients is 196 and the number of patients receiving study medication is 192.

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A Rituximab + Placebo

Arm description: -

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

Dosage and administration details:

Rituximab 375 mg/m² was administered weekly for 4 infusions on day 1 of week 1, 2, 3 and 4 and afterwards in 8-weekly intervals for 12 further infusions. The administration mode could have been changed to s.c. (1400 mg) in the maintenance phase dependent on the local standard of care.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to Ibrutinib was taken orally as capsules for 24 months (104 weeks) daily at approximately the same time every day.

Arm title	Arm B Rituximab + Ibrutinib
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab 375 mg/m² was administered weekly for 4 infusions on day 1 of week 1, 2, 3 and 4 and afterwards in 8-weekly intervals for 12 further infusions. The administration mode could have been changed to s.c. (1400 mg) in the maintenance phase dependent on the local standard of care.

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib was taken orally as capsules for 24 months (104 weeks) daily in a dose of 560 mg (4 x 140 mg capsules) at approximately the same time every day.

Number of subjects in period 1	Arm A Rituximab + Placebo	Arm B Rituximab + Ibrutinib
Started	98	98
Completed	98	94
Not completed	0	4
Not treated	-	4

Period 2

Period 2 title	Baseline
Is this the baseline period?	Yes ^[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
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Arm title	Arm A Rituximab + Placebo
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab 375 mg/m² was administered weekly for 4 infusions on day 1 of week 1, 2, 3 and 4 and afterwards in 8-weekly intervals for 12 further infusions. The administration mode could have been changed to s.c. (1400 mg) in the maintenance phase dependent on the local standard of care.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to Ibrutinib was taken orally as capsules for 24 months (104 weeks) daily at approximately the same time every day.

Arm title	Arm B Rituximab + Ibrutinib
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab 375 mg/m² was administered weekly for 4 infusions on day 1 of week 1, 2, 3 and 4 and afterwards in 8-weekly intervals for 12 further infusions. The administration mode could have been changed to s.c. (1400 mg) in the maintenance phase dependent on the local standard of care.

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib was taken orally as capsules for 24 months (104 weeks) daily in a dose of 560 mg (4 x 140 mg capsules) at approximately the same time every day.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Four of the randomized patients did not receive study treatment and thus were not included in the baseline period.

Number of subjects in period 2	Arm A Rituximab + Placebo	Arm B Rituximab + Ibrutinib
Started	98	94
Completed	98	94

Period 3

Period 3 title	Treatment and FU phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A Rituximab + Placebo

Arm description: -

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

Dosage and administration details:

Rituximab 375 mg/m² was administered weekly for 4 infusions on day 1 of week 1, 2, 3 and 4 and afterwards in 8-weekly intervals for 12 further infusions. The administration mode could have been changed to s.c. (1400 mg) in the maintenance phase dependent on the local standard of care.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to Ibrutinib was taken orally as capsules for 24 months (104 weeks) daily at approximately the same time every day.

Arm title	Arm B Rituximab + Ibrutinib
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab 375 mg/m² was administered weekly for 4 infusions on day 1 of week 1, 2, 3 and 4 and afterwards in 8-weekly intervals for 12 further infusions. The administration mode could have been changed to s.c. (1400 mg) in the maintenance phase dependent on the local standard of care.

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib was taken orally as capsules for 24 months (104 weeks) daily in a dose of 560 mg (4 x 140 mg capsules) at approximately the same time every day.

Number of subjects in period 3	Arm A Rituximab + Placebo	Arm B Rituximab + Ibrutinib
Started	98	94
Completed	86	84
Not completed	12	10
Consent withdrawn by subject	-	1
Death	9	7
Lost to follow-up	3	2

Baseline characteristics

Reporting groups

Reporting group title	Arm A Rituximab + Placebo
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Reporting group description: -

Reporting group title	Arm B Rituximab + Ibrutinib
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Reporting group description: -

Reporting group values	Arm A Rituximab + Placebo	Arm B Rituximab + Ibrutinib	Total
Number of subjects	98	94	192
Age categorical Units: Subjects			
Adults (18-64 years)	61	58	119
From 65-84 years	36	36	72
85 years and over	1	0	1
Gender categorical Units: Subjects			
Female	53	40	93
Male	45	54	99

End points

End points reporting groups

Reporting group title	Arm A Rituximab + Placebo
Reporting group description: -	
Reporting group title	Arm B Rituximab + Ibrutinib
Reporting group description: -	
Reporting group title	Arm A Rituximab + Placebo
Reporting group description: -	
Reporting group title	Arm B Rituximab + Ibrutinib
Reporting group description: -	
Reporting group title	Arm A Rituximab + Placebo
Reporting group description: -	
Reporting group title	Arm B Rituximab + Ibrutinib
Reporting group description: -	
Subject analysis set title	Arm A Rituximab + Placebo - FAS/PPS/SAF
Subject analysis set type	Full analysis
Subject analysis set description:	
There were no major protocol violations leading to an exclusion from one of the analysis sets. All randomized patients who started trial treatment qualified for inclusion in the Full Analysis Set (FAS), Per Protocol Set (PPS) and Safety Analysis Set (SAF).	
Subject analysis set title	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Subject analysis set type	Full analysis
Subject analysis set description:	
There were no major protocol violations leading to an exclusion from one of the analysis sets. All randomized patients who started trial treatment qualified for inclusion in the Full Analysis Set (FAS), Per Protocol Set (PPS) and Safety Analysis Set (SAF).	

Primary: PE | Complete response at 24 months (PET/CT)

End point title	PE Complete response at 24 months (PET/CT)
End point description:	
The primary endpoint is the proportion of patients with complete response (CR) at 24 months determined by PET/CT scan by the (independent response review) IRR panel.	
Progressive disease (PD) or death observed and the PD or death date $\leq$ 24 months after randomization >>> Non-CR	
No CR observed and last known non-PD and non-CR status date > 24 months >>> Non-CR	
1st CR date $\leq$ 24 months $\leq$ last CR date >>> CR	
End point type	Primary
End point timeframe:	
At 24 months	

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	94		
Units: patients with CR (%)				
number (confidence interval 95%)	35.7 (26.3 to 46.0)	40.4 (30.4 to 51.0)		

Statistical analyses

Statistical analysis title	Stratified logistic regression
Statistical analysis description: Comparson of CR at 24 months (by PET/CT) between treatment arms.	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.233 ^[2]
Method	stratified logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.799
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.46
Notes:	
[1] - Arm A vs B	
[2] - One-sided	

Primary: PE | Complete response at 24 months (PET/CT) - Sensitivity analyses

End point title	PE Complete response at 24 months (PET/CT) - Sensitivity analyses
End point description: The results for CR at 24 months as assessed by the (independent response review) IRR panel based on CT and PET alone are shown in Table 36 and Table 37. The analysis of the primary endpoint CR at 24 months was repeated with the response assessments entered by local investigators.	
End point type	Primary
End point timeframe: At 24 months.	

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	94		
Units: patients with CR (%)				
number (confidence interval 95%)				
CT alone	16.3 (9.6 to 25.2)	20.2 (12.6 to 29.8)		

PET alone	35.7 (26.3 to 46.0)	36.2 (26.5 to 46.7)		
PET/CT by local investigators	15.3 (8.8 to 24.0)	22.3 (14.4 to 32.1)		

Statistical analyses

Statistical analysis title	Stratified logistic regression - CT
Statistical analysis description:	
Comparson of CR at 24 months (by CT) between treatment arms	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.241 ^[4]
Method	stratified logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.766
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.61

Notes:

[3] - Arm A vs B

[4] - One-sided

Statistical analysis title	Stratified logistic regression - PET
Statistical analysis description:	
Comparson of CR at 24 months (by PET) between treatment arms	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.464 ^[6]
Method	stratified logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.972
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.8

Notes:

[5] - Arm A vs B

[6] - One-sided

Statistical analysis title	Stratified logistic regression - local inv.
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Statistical analysis description:

Comparson of CR at 24 months (by local investigators) between treatment arms

Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[7]
P-value	= 0.099 ^[8]
Method	stratified logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.613
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.29

Notes:

[7] - Arm A vs B

[8] - One-sided

Secondary: SE | Complete response at 30 months (PET/CT)

End point title	SE Complete response at 30 months (PET/CT)
End point description:	
Any assessment within a window of week 126 to week 142 (inclusive) was considered as the 30 months response assessment for determining the CR status. The same rules as described for the primary endpoint were used for determination of CR status at 30 months.	
End point type	Secondary
End point timeframe:	
At 30 months.	

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	94		
Units: patients (%) with CR				
number (confidence interval 95%)	28.6 (19.9 to 38.6)	34.0 (24.6 to 44.5)		

Statistical analyses

Statistical analysis title	Stratified logistic regression
Statistical analysis description:	
Between arm comparison of CR at 30 months	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF

Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	= 0.427
Method	stratified logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.46

Notes:

[9] - Arm A vs B

Secondary: SE | Evaluation of minimal residual disease (MRD) - bone marrow

End point title	SE Evaluation of minimal residual disease (MRD) - bone marrow
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End point description:

MRD evaluation was performed using real-time PCR (polymerase chain reaction) based methods in peripheral blood and bone marrow at baseline and week 106. The proportion of patients achieving MRD negativity at week 106 was calculated separately for bone marrow and peripheral blood. Only patients with positive MRD at baseline were considered for this analysis. Due to the low sample sizes, no statistical comparison (logistic regression) between treatment arms has been performed.

End point type	Secondary
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End point timeframe:

At week 106.

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3 ^[10]	6 ^[11]		
Units: patients (%) with MRD negativity				
number (not applicable)				
negative	100.0	83.3		
positive	0.0	16.7		

Notes:

[10] - Only for patients with data at baseline and week 106.

[11] - Only for patients with data at baseline and week 106.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Evaluation of minimal residual disease (MRD) - peripheral blood

End point title	SE Evaluation of minimal residual disease (MRD) - peripheral blood
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End point description:

MRD evaluation was performed using real-time PCR (polymerase chain reaction) based methods in

peripheral blood and bone marrow at baseline and week 106. The proportion of patients achieving MRD negativity at week 106 was calculated separately for bone marrow and peripheral blood. Only patients with positive MRD at baseline were considered for this analysis. Due to the low sample sizes, no statistical comparison (logistic regression) between treatment arms has been performed.

End point type	Secondary
End point timeframe:	
At week 106.	

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 ^[12]	25 ^[13]		
Units: patients (%) with MRD negativity				
number (not applicable)				
Negative	100.0	96.0		
Positive	0.0	4.0		

Notes:

[12] - Only for patients with data at baseline and week 106.

[13] - Only for patients with data at baseline and week 106.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Overall response (OR) at 24 weeks

End point title	SE Overall response (OR) at 24 weeks
End point description:	
Overall response (OR) is defined as either:	
- the disappearance of all evidence of disease (CR)	
- the regression of measurable disease with no new sites (PR)	
Any assessment within a window of 21 to 27 weeks (inclusive) was considered as the 24 weeks response assessment for determining the OR status. Similar rules as described for the primary endpoint were used for determination of OR status at 24 weeks in case of missing assessment within a window of 21 to 27 weeks. For this endpoint, data entered by the local investigators were used.	
End point type	Secondary
End point timeframe:	
At 24 weeks.	

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	94		
Units: patients (%) with OR				
number (confidence interval 95%)	59.2 (48.8 to 69.0)	73.4 (63.3 to 82.0)		

Statistical analyses

Statistical analysis title	Stratified logistic regression
Statistical analysis description: Between arm comparison of OR at 24 weeks	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[14]
P-value	= 0.046
Method	stratified logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.99

Notes:

[14] - Arm A vs B

Secondary: SE | Duration of complete response (DUR)

End point title	SE Duration of complete response (DUR)
End point description: Kaplan-Meier analysis.	
DUR was calculated from when the criteria for CR (according to local assessments recorded on the tumor form) were met, until documentation of relapse thereafter. Only patients with a CR (n=56) were included in this analysis. Patients without any documentation of relapse thereafter were censored at the last time they were known to be without relapse (i.e. last date of tumor assessment without relapse) and before the start of a new anti-lymphoma treatment, if any.	
A total of 9 patients experienced an event in Arm A and 6 in Arm B.	
Note: Median and upper 95% confidence intervall were not reached for both arms. Dummy data ("9999") entered due to database restrictions.	
End point type	Secondary
End point timeframe: From achieving criteria for CR until documentation of relapse thereafter.	

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 ^[15]	32 ^[16]		
Units: months				
median (confidence interval 95%)	9999 (20.8 to 9999)	9999 (49.4 to 9999)		

Notes:

[15] - Only for patients achieving CR.

[16] - Only for patients achieving CR.

Statistical analyses

Statistical analysis title	Stratified Cox proportional hazards model
Statistical analysis description: Between arm comparison of DUR months.	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other ^[17]
P-value	= 0.454
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.06

Notes:

[17] - Arm B vs A

Secondary: SE | Progression-free survival (PFS)

End point title	SE Progression-free survival (PFS)
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End point description:

Kaplan-Meier analysis.

Progression-free survival (PFS) was calculated from randomization until the first event of interest:

- disease progression or relapse
- death from any cause

Patients not experiencing an event, including patients receiving a subsequent anti-lymphoma therapy without documented disease progression or relapse, were censored at the last time they were known to be without progression (i.e. last date of tumor assessment without progression) and before the start of a new anti-lymphoma treatment, if any.

A total of 48 patients experienced a PFS event in Arm A and 36 in Arm B.

Note: Upper 95%-CI for arm B was not reached. Dummy data ("9999") entered due to database restrictions.

End point type	Secondary
End point timeframe:	
From baseline until disease progression or relapse or death from any cause.	

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	94		
Units: months				
median (confidence interval 95%)	32.7 (24.6 to 55.0)	61.9 (33.1 to 9999)		

Statistical analyses

Statistical analysis title	Stratified Cox proportional hazards model
Statistical analysis description: Between arm comparison of PFS months.	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	= 0.057
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.01

Notes:

[18] - Arm B vs A

Secondary: SE | Event-free survival (EFS)

End point title	SE Event-free survival (EFS)
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End point description:

Kaplan-Meier analysis.

Event-free survival (time to treatment failure) was calculated from randomization to premature discontinuation of trial treatment for any reason (e.g., insufficient response at first, second or third restaging at 12, 24 or 52 weeks, progressive disease, toxicity, patient preference, initiation of new anti-lymphoma treatment without documented progression, secondary malignancy or death). After completion of trial therapy the following was considered as event: progressive disease, death, initiation of new anti-lymphoma treatment without documented progression or secondary malignancy. Patients not experiencing an event will were censored at the last date they were known to be alive.

A total of 70 patients experienced an EFS event in Arm A and 56 in Arm B.

End point type	Secondary
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End point timeframe:

From randomization to premature discontinuation of trial treatment for any reason.

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	94		
Units: months				
median (confidence interval 95%)	21.6 (11.1 to 24.8)	30.2 (17.9 to 61.0)		

Statistical analyses

Statistical analysis title	Stratified Cox proportional hazards model
Statistical analysis description: Between arm comparison of EFS months.	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[19]
P-value	= 0.053
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1

Notes:

[19] - Arm B vs A

Secondary: SE | Time to next anti-lymphoma therapy (TTNT)

End point title	SE Time to next anti-lymphoma therapy (TTNT)
End point description: Kaplan-Meier analysis.	
Time to next anti-lymphoma therapy (TTNT) was calculated from randomization until the start of the first off-trial anti-lymphoma treatment. Patients not receiving any off-trial anti-lymphoma treatment were censored at the last follow-up visit.	
A total of 52 patients experienced a TTNT event in Arm A and 43 in Arm B.	
Note: Upper 95%-CI not reached for arm A and B. Dummy data ("9999") entered due to database restrictions.	
End point type	Secondary

End point timeframe:

From randomization until the start of the first off-trial anti-lymphoma treatment.

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	94		
Units: months				
median (confidence interval 95%)	41.2 (24.0 to 9999)	73.8 (33.1 to 9999)		

Statistical analyses

Statistical analysis title	Stratified Cox proportional hazards model
Statistical analysis description: Between arm comparison of TTNT months.	
Comparison groups	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF v Arm A Rituximab + Placebo - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[20]
P-value	= 0.112
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.09

Notes:

[20] - Arm B vs A

Secondary: SE | Overall survival (OS)

End point title	SE Overall survival (OS)
End point description: Kaplan-Meier analysis.	
OS was calculated from randomization until death. Patients not experiencing an event were censored at the last date they were known to be alive.	
A total of 9 patients died in Arm A and 7 in Arm B.	
Note: Median and upper 95%-CI for arm A and B, and additionally the lower 95%-CI for arm A were not reached. Dummy data ("9999") entered due to database restrictions.	
End point type	Secondary
End point timeframe: From randomization until death.	

End point values	Arm A Rituximab + Placebo - FAS/PPS/SAF	Arm B Rituximab + Ibrutinib - FAS/PPS/SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	94		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (75.3 to 9999)		

Statistical analyses

Statistical analysis title	Stratified Cox proportional hazards model
Statistical analysis description: Between arm comparison of OS months.	
Comparison groups	Arm A Rituximab + Placebo - FAS/PPS/SAF v Arm B Rituximab + Ibrutinib - FAS/PPS/SAF
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other ^[21]
P-value	= 0.81
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.56

Notes:

[21] - Arm B vs A

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE reporting period is from registration into the trial until 30 days after end of treatment (or immediately prior to next off-trial treatment, whichever occurs first).

Adverse event reporting additional description:

Ongoing AEs need to be followed-up until resolution or permanent sequelae or start of new therapy.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Arm A Rituximab + Placebo
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Reporting group description: -

Reporting group title	Arm B Rituximab + Ibrutinib
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Reporting group description: -

Serious adverse events	Arm A Rituximab + Placebo	Arm B Rituximab + Ibrutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 98 (25.51%)	37 / 94 (39.36%)	
number of deaths (all causes)	9	7	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	2 / 98 (2.04%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 98 (1.02%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	1 / 98 (1.02%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma transformation	Additional description: Arm A: 6 events for 6 patients (Diffuse large B-cell lymphoma) Arm B: 8 events for 8 patients (Diffuse large B-cell lymphoma), 1 event for 1 patient (High-grade B-cell lymphoma), 2 events for 2 patients (Hodgkin's disease).		
subjects affected / exposed	6 / 98 (6.12%)	11 / 94 (11.70%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung adenocarcinoma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant sweat gland neoplasm			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 98 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			

subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cyst removal	Additional description: Removal of branchial cleft cyst (right side).		
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillectomy	Additional description: Tonsillectomy and biopsy of throat cyst.		
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serum sickness			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chylothorax			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased	Additional description: Aspartate aminotransferase and alanine aminotransferase increased increased for both patients.		

subjects affected / exposed	1 / 98 (1.02%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 98 (1.02%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ventricular tachycardia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (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	1 / 98 (1.02%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 98 (1.02%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (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			
Abdominal infection			

subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 98 (0.00%)	4 / 94 (4.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 98 (1.02%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 98 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A Rituximab + Placebo	Arm B Rituximab + Ibrutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 98 (100.00%)	94 / 94 (100.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	6 / 98 (6.12%)	11 / 94 (11.70%)	
occurrences (all)	6	12	
Hypertension			
subjects affected / exposed	11 / 98 (11.22%)	11 / 94 (11.70%)	
occurrences (all)	21	19	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	11 / 98 (11.22%)	4 / 94 (4.26%)	
occurrences (all)	13	4	
Fatigue			
subjects affected / exposed	32 / 98 (32.65%)	34 / 94 (36.17%)	
occurrences (all)	39	47	
Pyrexia			
subjects affected / exposed	7 / 98 (7.14%)	9 / 94 (9.57%)	
occurrences (all)	7	9	
Influenza like illness			
subjects affected / exposed	16 / 98 (16.33%)	18 / 94 (19.15%)	
occurrences (all)	23	22	
Pain			
subjects affected / exposed	9 / 98 (9.18%)	12 / 94 (12.77%)	
occurrences (all)	11	18	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed occurrences (all)	18 / 98 (18.37%) 27	29 / 94 (30.85%) 38	
Dyspnoea subjects affected / exposed occurrences (all)	11 / 98 (11.22%) 11	6 / 94 (6.38%) 7	
Epistaxis subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 2	9 / 94 (9.57%) 9	
Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 10	6 / 94 (6.38%) 7	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	6 / 94 (6.38%) 6	
Insomnia subjects affected / exposed occurrences (all)	8 / 98 (8.16%) 8	7 / 94 (7.45%) 12	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	29 / 98 (29.59%) 158	24 / 94 (25.53%) 85	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	29 / 98 (29.59%) 153	20 / 94 (21.28%) 82	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	32 / 98 (32.65%) 129	31 / 94 (32.98%) 98	
Blood bilirubin increased subjects affected / exposed occurrences (all)	12 / 98 (12.24%) 39	25 / 94 (26.60%) 187	
Blood creatinine increased subjects affected / exposed occurrences (all)	34 / 98 (34.69%) 166	29 / 94 (30.85%) 232	
Lymphocyte count decreased			

subjects affected / exposed occurrences (all)	59 / 98 (60.20%) 470	49 / 94 (52.13%) 387	
Neutrophil count decreased subjects affected / exposed occurrences (all)	16 / 98 (16.33%) 38	34 / 94 (36.17%) 61	
Platelet count decreased subjects affected / exposed occurrences (all)	26 / 98 (26.53%) 128	45 / 94 (47.87%) 424	
White blood cell count decreased subjects affected / exposed occurrences (all)	19 / 98 (19.39%) 49	16 / 94 (17.02%) 27	
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	12 / 98 (12.24%) 17	4 / 94 (4.26%) 4	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	10 / 98 (10.20%) 13	7 / 94 (7.45%) 7	
Dysgeusia subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 5	1 / 94 (1.06%) 1	
Headache subjects affected / exposed occurrences (all)	15 / 98 (15.31%) 27	21 / 94 (22.34%) 30	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	42 / 98 (42.86%) 220	41 / 94 (43.62%) 215	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	6 / 94 (6.38%) 7	
Gastrointestinal disorders Abdominal pain			

subjects affected / exposed	14 / 98 (14.29%)	12 / 94 (12.77%)	
occurrences (all)	21	22	
Constipation			
subjects affected / exposed	5 / 98 (5.10%)	10 / 94 (10.64%)	
occurrences (all)	6	11	
Diarrhoea			
subjects affected / exposed	27 / 98 (27.55%)	30 / 94 (31.91%)	
occurrences (all)	40	52	
Dry mouth			
subjects affected / exposed	6 / 98 (6.12%)	7 / 94 (7.45%)	
occurrences (all)	6	7	
Dyspepsia			
subjects affected / exposed	3 / 98 (3.06%)	10 / 94 (10.64%)	
occurrences (all)	3	12	
Gastritis			
subjects affected / exposed	0 / 98 (0.00%)	7 / 94 (7.45%)	
occurrences (all)	0	7	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 98 (1.02%)	7 / 94 (7.45%)	
occurrences (all)	1	7	
Stomatitis			
subjects affected / exposed	3 / 98 (3.06%)	6 / 94 (6.38%)	
occurrences (all)	3	9	
Nausea			
subjects affected / exposed	19 / 98 (19.39%)	20 / 94 (21.28%)	
occurrences (all)	32	34	
Abdominal pain upper			
subjects affected / exposed	9 / 98 (9.18%)	3 / 94 (3.19%)	
occurrences (all)	10	5	
Vomiting			
subjects affected / exposed	6 / 98 (6.12%)	6 / 94 (6.38%)	
occurrences (all)	6	9	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	6 / 98 (6.12%)	8 / 94 (8.51%)	
occurrences (all)	7	9	

Pruritus subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 7	5 / 94 (5.32%) 7	
Rash maculo-papular subjects affected / exposed occurrences (all)	8 / 98 (8.16%) 10	21 / 94 (22.34%) 28	
Renal and urinary disorders Chronic kidney disease subjects affected / exposed occurrences (all)	75 / 98 (76.53%) 1140	83 / 94 (88.30%) 1256	
Pollakiuria subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 4	5 / 94 (5.32%) 6	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	13 / 98 (13.27%) 17	7 / 94 (7.45%) 7	
Back pain subjects affected / exposed occurrences (all)	14 / 98 (14.29%) 17	15 / 94 (15.96%) 20	
Muscle spasms subjects affected / exposed occurrences (all)	2 / 98 (2.04%) 2	9 / 94 (9.57%) 13	
Myalgia subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 6	4 / 94 (4.26%) 5	
Pain in extremity subjects affected / exposed occurrences (all)	10 / 98 (10.20%) 10	14 / 94 (14.89%) 17	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	2 / 98 (2.04%) 2	5 / 94 (5.32%) 6	
COVID-19 subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 6	3 / 94 (3.19%) 4	

Lip infection			
subjects affected / exposed	3 / 98 (3.06%)	5 / 94 (5.32%)	
occurrences (all)	6	6	
Pneumonia			
subjects affected / exposed	0 / 98 (0.00%)	5 / 94 (5.32%)	
occurrences (all)	0	6	
Nail infection			
subjects affected / exposed	1 / 98 (1.02%)	5 / 94 (5.32%)	
occurrences (all)	1	5	
Rhinitis			
subjects affected / exposed	3 / 98 (3.06%)	5 / 94 (5.32%)	
occurrences (all)	4	6	
Skin infection			
subjects affected / exposed	2 / 98 (2.04%)	7 / 94 (7.45%)	
occurrences (all)	2	7	
Upper respiratory tract infection			
subjects affected / exposed	13 / 98 (13.27%)	10 / 94 (10.64%)	
occurrences (all)	14	13	
Urinary tract infection			
subjects affected / exposed	5 / 98 (5.10%)	4 / 94 (4.26%)	
occurrences (all)	10	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 98 (8.16%)	9 / 94 (9.57%)	
occurrences (all)	8	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2016	A substantial amendment has been issued in order to adapt the Serious Adverse Event definition and reporting in the protocol. Further changes: - Risk changes: due to the new IB of Ibrutinib (Version 9, 30th June 2015) the chapter "drug related adverse events" (section 10.3) of the protocol was updated. - Adaptations to answer conditions issued by the Norwegian Medicines Agency - Administrative changes, clarifications and inconsistencies: correction of typos and wording
23 December 2016	A substantial amendment has been issued. The main reason for the amendment was the update of the risk section of the protocol and of the PIS/IC documents due to the release of the new IB of Ibrutinib (Version 10, 29th August 2016). Summary of changes: - Risk section: the chapter "drug related adverse events" (section 10.3) of the protocol was updated according to the new IB of Ibrutinib (Version 10, 29th August 2016). - Exclusion criteria: patient treatment with Aspirin up to 300 mg/daily is now allowed (section 6.2). - Translational research projects for the Biobank in Norway and Sweden: minor modifications were made concerning sample collections: amount and less time points (section 18.1). - Trial summary: has been integrated directly into the protocol. - Swiss Specific Appendix: description on how to order Rituximab provided by Roche in Switzerland. - Administrative changes, clarifications and inconsistencies: correction of typos and wording.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported