Clinical trial results:
Nivolumab and AVD in early-stage unfavorable classical Hodgkin lymphoma - A GHSG randomized, multicenter phase II trial

Summary

EudraCT number	2016-002626-37
Trial protocol	DE
Global end of trial date	20 July 2022

Results information

Result version number	v1 (current)
This version publication date	07 July 2023
First version publication date	07 July 2023

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-2854

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03004833
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Köln, Germany, 50923
Public contact	Trial Coordination Center, German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de
Scientific contact	Trial Coordination Center, German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de

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	03 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate efficacy of the 2 experimental strategies in patients with early-stage unfavorable cHL. Secondary objectives were to describe safety, long-term efficacy and feasibility of both strategies.

Protection of trial subjects:

Written informed consent before study entry, frequent IDMC monitoring, central response evaluation

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 April 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 110
Worldwide total number of subjects	110
EEA total number of subjects	110

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)	110
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 19 Apr 2017 and 30 Oct 2018, 110 patients were enrolled in 28 trial sites in Germany.

Pre-assignment

Screening details:

Main entry criteria were histologically proven first diagnosis of classical Hodgkin lymphoma (cHL), no previous treatment for cHL, age at enrollment 18-60 years, clinical stage I or II with risk factors.

Period 1

Period 1 title	Enrollment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Concomitant therapy

Arm description:

Concomitant therapy with Nivolumab and AVD (N-AVD) on day 1 and 15 of each 28-day cycle for 4 cycles, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).

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

Dosage and administration details:

240 mg on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

25 mg/m² BSA on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

6 mg/m² BSA on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

375 mg/m² BSA on day 1 and 15 of each 28-day cycle

Arm title	Sequential therapy

Arm description:

Sequential therapy starting with 4 infusions of nivolumab in 14-day intervals followed by two 28-day cycles N-AVD and two 28-day cycles AVD, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).

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

Dosage and administration details:

240 mg on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

25 mg/m² BSA on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

6 mg/m² BSA on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

375 mg/m² BSA on day 1 and 15 of each 28-day cycle

Number of subjects in period 1	Concomitant therapy	Sequential therapy
Started	55	55
Completed	55	54
Not completed	0	1
Disconfirmation of diagnosis	-	1

Period 2

Period 2 title	Full analysis set
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Concomitant therapy

Arm description:

Concomitant therapy with Nivolumab and AVD (N-AVD) on day 1 and 15 of each 28-day cycle for 4 cycles, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).

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

Dosage and administration details:

240 mg on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

25 mg/m² BSA on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

6 mg/m² BSA on day 1 and 15 of each 28-day cycle

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

Dosage and administration details:

375 mg/m² BSA on day 1 and 15 of each 28-day cycle

Arm title	Sequential therapy

Arm description:

Sequential therapy starting with 4 infusions of nivolumab in 14-day intervals followed by two 28-day cycles N-AVD and two 28-day cycles AVD, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).

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

Dosage and administration details:	
240 mg on day 1 and 15 of each 28-day cycle	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
25 mg/m² BSA on day 1 and 15 of each 28-day cycle	
Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use
Dosage and administration details:	
6 mg/m² BSA on day 1 and 15 of each 28-day cycle	
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
375 mg/m² BSA on day 1 and 15 of each 28-day cycle	

Notes:

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

Justification: Patients with disconfirmed cHL diagnosis were excluded from all analyses are not reported in the baseline period.

Number of subjects in period 2[2]	Concomitant therapy	Sequential therapy
Started	55	54
Completed	51	50
Not completed	4	4
False risk-group allocation	-	1
Adverse event, non-fatal	3	2
Participant's wish	1	1

Notes:

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

Justification: Patients with disconfirmed cHL diagnosis were excluded from all analyses are not reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Concomitant therapy
Reporting group description:	
Concomitant therapy with Nivolumab and AVD (N-AVD) on day 1 and 15 of each 28-day cycle for 4 cycles, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).	
Reporting group title	Sequential therapy
Reporting group description:	
Sequential therapy starting with 4 infusions of nivolumab in 14-day intervals followed by two 28-day cycles N-AVD and two 28-day cycles AVD, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).	

Reporting group values	Concomitant therapy	Sequential therapy	Total
Number of subjects	55	54	109
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	55	54	109
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	26	27	
full range (min-max)	18 to 57	18 to 60	-
Gender categorical Units: Subjects			
Female	32	33	65
Male	23	21	44
ECOG performance status Units: Subjects			
ECOG=0	42	41	83
ECOG=1	13	13	26
Histologic subtype Units: Subjects			
NS cHL	33	36	69
MC cHL	6	7	13
LR cHL	2	1	3
cHL unspecified	13	10	23
Unknown	1	0	1
Ann Arbor Stage Units: Subjects			
IA	3	1	4

IB	0	1	1
IIA	41	41	82
IIB	11	11	22
Risk factor large mediastinal mass Units: Subjects			
Yes	7	15	22
No	48	39	87
Risk factor extranodal disease Units: Subjects			
Yes	8	6	14
No	47	48	95
Risk factor elevated ESR Units: Subjects			
Yes	25	27	52
No	30	27	57
Risk factor 3 or more nodal areas involved Units: Subjects			
Yes	39	36	75
No	16	18	34

End points

End points reporting groups

Reporting group title	Concomitant therapy

Reporting group description:

Concomitant therapy with Nivolumab and AVD (N-AVD) on day 1 and 15 of each 28-day cycle for 4 cycles, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).

Reporting group title	Sequential therapy

Reporting group description:

Sequential therapy starting with 4 infusions of nivolumab in 14-day intervals followed by two 28-day cycles N-AVD and two 28-day cycles AVD, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).

Reporting group title	Concomitant therapy

Reporting group description:

Concomitant therapy with Nivolumab and AVD (N-AVD) on day 1 and 15 of each 28-day cycle for 4 cycles, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).

Reporting group title	Sequential therapy

Reporting group description:

Sequential therapy starting with 4 infusions of nivolumab in 14-day intervals followed by two 28-day cycles N-AVD and two 28-day cycles AVD, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT).

Subject analysis set title	Efficacy analysis set - Concomitant therapy
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy analysis set (EAS) consists of all patients from the full analysis set who are evaluable for the primary efficacy endpoint. Patients are not evaluable for the primary endpoint and therefore excluded from the EAS in the following cases:

- Major protocol deviation (< 3 full cycles of AVD or < 4 doses of nivolumab or administration of any non-protocol therapy) for reasons other than progressive disease or inadequate response
- There is evidence that the patient is not qualified for the trial, based on data obtained before study entry (e.g., histology, staging, case history or previous treatment)
- Change of treatment group at any time

Subject analysis set title	Efficacy analysis set - sequential therapy
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy analysis set (EAS) consists of all patients from the full analysis set who are evaluable for the primary efficacy endpoint. Patients are not evaluable for the primary endpoint and therefore excluded from the EAS in the following cases:

- Major protocol deviation (< 3 full cycles of AVD or < 4 doses of nivolumab or administration of any non-protocol therapy) for reasons other than progressive disease or inadequate response
- There is evidence that the patient is not qualified for the trial, based on data obtained before study entry (e.g., histology, staging, case history or previous treatment)

Primary: Complete remission rate

End point title	Complete remission rate[1]

End point description:

The complete remission (CR) rate was defined as the proportion of patients showing a complete tumor response in the centrally reviewed final restaging after completion of protocol treatment including IS-RT. A complete remission has been attained if one of the following conditions was met:

- Complete radiologic response with regress of all residual masses to ≤ 1.5 cm in the largest diameter in absence of signs of active lymphoma
- Complete metabolic response (score 1-3) with or without residual masses in absence of clinical signs of active lymphoma
- No signs of active lymphoma and CR already achieved in an earlier restaging

End point type	Primary

End point timeframe:

Response was measured at the final restaging after completion of protocol treatment including IS-RT.

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 is a phase-2 trial with 2 regimens to be evaluated independently. There is no arm comparison but 2 single-arm analyses, which cannot be entered in the system.
Analyses were as follows:
The null hypothesis "CR rate<=80%" was tested against a one-sided alternative via a one-sided 97.5% CI per arm.
The lower confidence limits were 79% for concomitant and 84% for sequential therapy, respectively.
Thus, the 80% benchmark was narrowly missed in the concomitant and met in the sequential group.

End point values	Efficacy analysis set - Concomitant therapy	Efficacy analysis set - sequential therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51[2]	50[3]		
Units: patients				
CR	46	47		
Non-CR	5	3		

Notes:

[2] - Reasons for exclusion from primary endpoint analysis were AEs (n=3) and participant's wish (n=1)

[3] - Reasons for exclusion were AEs (n=2), false risk-group allocation (n=1) and participant's wish (n=1

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival is defined as time between the date of randomization and the date of first progression, relapse, or death or, in cases of continuing response, the date of the last documented follow-up.

End point type	Secondary

End point timeframe:

3-year progression-free survival will be reported

End point values	Concomitant therapy	Sequential therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	54		
Units: percent				
number (confidence interval 95%)	100 (100 to 100)	98 (95 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival is defined as time between the date of randomization and the date of death. If the patient is alive at the time of analysis, overall survival will be censored on the date of the last documented information on survival status.

End point type	Secondary

End point timeframe:

Overall survival after 3 years will be reported

End point values	Concomitant therapy	Sequential therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	54		
Units: percent				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All events up to 30 days after end of treatment had to be reported. Events that occured later than 30 days after the end of treatment had to be reported if causality was rated at least as “possible”.

Adverse event reporting additional description:

AEs were assessed on the therapy administration CRFs. SAEs were additionally assessed on specific forms. SAEs may thus be reported twice; non-serious AEs might contain SAEs; non-serious and SAEs might not add up to a total number of AEs.
All AEs of CTCAE grade >=1 will be reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Concomitant therapy

Reporting group description:

Concomitant therapy with Nivolumab and AVD (N-AVD) on day 1 and 15 of each 28-day cycle for 4 cycles,followed by consolidating 30 Gy involved-site radiotherapy (IS-RT)

Reporting group title	Sequential therapy

Reporting group description:

Sequential therapy starting with 4 infusions of nivolumab in 14-day intervals followed by two 28-day cycles N-AVD and two 28-day cycles AVD, followed by consolidating 30 Gy involved-site radiotherapy (IS-RT)

Serious adverse events	Concomitant therapy	Sequential therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 55 (38.18%)	15 / 54 (27.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Vascular disorders	Additional description: Includes Pulmonary embolism, Vena cava thrombosis		
subjects affected / exposed	1 / 55 (1.82%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: Includes Mucosal inflammation, Pyrexia, General physical health deterioration, Non-cardiac chest pain		
subjects affected / exposed	6 / 55 (10.91%)	3 / 54 (5.56%)	
occurrences causally related to treatment / all	9 / 9	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (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			
Respiratory, thoracic and mediastinal disorders	Additional description: Includes Pneumothorax, Tonsillitis, Upper respiratory tract infection		
subjects affected / exposed	2 / 55 (3.64%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders	Additional description: Includes Meningitis, Polyneuropathy		
subjects affected / exposed	1 / 55 (1.82%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: Includes Febrile neutropenia, Neutropenia		
subjects affected / exposed	7 / 55 (12.73%)	4 / 54 (7.41%)	
occurrences causally related to treatment / all	7 / 7	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: Includes Abdominal pain, Diarrhoea, Dysphagia, Enterocolitis, Gastritis, Gastroenteritis, Nausea, Pancreatitis, Vomiting		
subjects affected / exposed	4 / 55 (7.27%)	4 / 54 (7.41%)	
occurrences causally related to treatment / all	4 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: Includes AI hepatitis, Hepatitis		
subjects affected / exposed	0 / 55 (0.00%)	2 / 54 (3.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: Includes Pruritus, Rash		

subjects affected / exposed	1 / 55 (1.82%)	2 / 54 (3.70%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urogenital disorder			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations	Additional description: Includes Infection, Febrile infection		
subjects affected / exposed	2 / 55 (3.64%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Concomitant therapy	Sequential therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 55 (98.18%)	53 / 54 (98.15%)	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	1 / 55 (1.82%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
Nervous system disorders			

Nervous system disorder			
subjects affected / exposed	23 / 55 (41.82%)	18 / 54 (33.33%)	
occurrences (all)	48	34	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	50 / 55 (90.91%)	45 / 54 (83.33%)	
occurrences (all)	148	165	
Thrombocytopenia			
subjects affected / exposed	11 / 55 (20.00%)	11 / 54 (20.37%)	
occurrences (all)	18	27	
Leukopenia			
subjects affected / exposed	49 / 55 (89.09%)	46 / 54 (85.19%)	
occurrences (all)	144	160	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 55 (10.91%)	11 / 54 (20.37%)	
occurrences (all)	6	16	
Allergy			
subjects affected / exposed	1 / 55 (1.82%)	2 / 54 (3.70%)	
occurrences (all)	3	2	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	12 / 55 (21.82%)	21 / 54 (38.89%)	
occurrences (all)	23	39	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	41 / 55 (74.55%)	37 / 54 (68.52%)	
occurrences (all)	97	87	
Mucositis			
subjects affected / exposed	14 / 55 (25.45%)	19 / 54 (35.19%)	
occurrences (all)	24	36	
Gastrointestinal disorders			
subjects affected / exposed	28 / 55 (50.91%)	19 / 54 (35.19%)	
occurrences (all)	43	41	
Dysphagia			

subjects affected / exposed	2 / 55 (3.64%)	4 / 54 (7.41%)	
occurrences (all)	2	4	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	12 / 55 (21.82%)	13 / 54 (24.07%)	
occurrences (all)	15	17	
Hepatobiliary disorders			
Hepatobiliary disorder			
subjects affected / exposed	27 / 55 (49.09%)	28 / 54 (51.85%)	
occurrences (all)	48	66	
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	23 / 55 (41.82%)	31 / 54 (57.41%)	
occurrences (all)	42	65	
Renal and urinary disorders			
Urogenital disorder			
subjects affected / exposed	4 / 55 (7.27%)	4 / 54 (7.41%)	
occurrences (all)	4	7	
Renal disorder			
subjects affected / exposed	4 / 55 (7.27%)	2 / 54 (3.70%)	
occurrences (all)	5	3	
Infections and infestations			
Infection			
subjects affected / exposed	25 / 55 (45.45%)	23 / 54 (42.59%)	
occurrences (all)	34	36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2017	Within the framework of the Amendment, updates due to a new version of the IB and editorial / organizational changes were implemented.
11 December 2017	Within the framework of this amendment, a mandatory antiphlogistic and antiemetic concomitant medication and additional measures to increase safety of trial participants were established and editorial changes implemented.
20 September 2018	Within the framework of the Amendment, updates due to a new version of the IB and editorial / organizational changes were implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32352505

http://www.ncbi.nlm.nih.gov/pubmed/36508302