Clinical trial results:
A Phase I/II Open-Label, Non-Randomized Dose Escalation Study of Immunoconjugate L-DOS47 as a Monotherapy in Non-Squamous Non-Small Cell Lung Cancer Patients

Summary

EudraCT number	2010-020729-42
Trial protocol	PL
Global end of trial date	30 December 2017

Results information

Result version number	v1 (current)
This version publication date	09 October 2020
First version publication date	09 October 2020
Summary attachment (see zip file)	Synopsis (LDOS002 Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	LDOS002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02340208
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Helix BioPharma Corp.
Sponsor organisation address	9120 Leslie Street, Suite 205, Richmond Hill, Canada, L4B 3J9
Public contact	Chief Executive Officer, Helix BioPharma Corp., +1 905 717 3280 , hchao@helixbiopharma.com
Scientific contact	Clinical Operations Director, Helix BioPharma Corp., +1 905-841-2300x282, blee@helixbiopharma.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	07 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I
- To define the maximum tolerated doses of multiple doses of L-DOS47 administered intravenously to patients with non-squamous non-small cell lung cancer when given as monotherapy.
Phase II
- To make a preliminary assessment of the efficacy of L-DOS47 in patients with non-squamous non-small cell lung cancer.

Protection of trial subjects:

During the Phase I dose escalation portion of the study, patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort. In order to monitor and assess possible infusion reactions and/or allergic reactions, the first dosing cohort was dosed 8 days before subsequent patients were dosed. Furthermore, simultaneous dosing of patients within each cohort in the Phase I portion was prohibited. For each cohort, patient dosing was separated by at least 24 hours. This further allowed the assessment for possible infusion reactions and/or allergic reactions and enable communication between study centres. All patients at a given dose level also had to complete Cycle 1 (3-week period) before escalation in subsequent patients could proceed. The decision for dose escalation to the next dose level was made after the safety data had been reviewed by the Trial Steering Committee, which was composed of site investigators and the sponsor medical monitor.

The Phase II portion of the study employed the decision rules and enrolment strategy based on Simon's optimal two-stage design in order to be able assess preliminary efficacy while minimizing number of subjects to be enrolled.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	15 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 76
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	49
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the Phase I dose escalation, patients were recruited at four different sites situated in Poland between September 2012 and March 2016. In Phase II, patients were recruited at three sites situated in Poland between April 2016 and April 2017.

Pre-assignment

Screening details:

Adults with histologically confirmed Stage IIIb or IV NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; life expectancy ≥3 months; not receiving radiotherapy (except symptomatic treatment of bone metastases), targeted therapy, hormonal therapy or immunotherapy, major surgery or other study drugs within prior 4 weeks

Period 1

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	L-DOS47 0.12 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 0.21 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 0.33 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 0.46 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 0.59 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 0.78 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with

sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 1.04 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 1.38 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 1.84 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 2.45 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental

Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 3.26 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 4.33 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 5.76 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 7.66 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per

cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 10.19 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 13.55 µg/kg_Phase I

Arm description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion on days 1 and 8 of each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as well tolerated with sustained clinical benefit, in the opinion of the clinical investigator.

Arm title	L-DOS47 13.55 µg/kg_Phase II

Arm description:

An initial 17 evaluable patients, based on Simon's optimal two-stage design, will be enrolled in the first stage. If ≥ 1 response, a further 22 patients would be enrolled in the second stage.

Arm type	Experimental
Investigational medicinal product name	L-DOS47
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered L-DOS47 by IV infusion twice weekly on days 1, 4, 8 and 11 followed 7 days' rest in each 21-day treatment cycle for four treatment cycles, after which patients may continue to receive two additional cycles as long as there was sustained clinical benefit and well tolerated, in the opinion of the clinical investigator.

Number of subjects in period 1	L-DOS47 0.12 µg/kg_Phase I	L-DOS47 0.21 µg/kg_Phase I	L-DOS47 0.33 µg/kg_Phase I
Started	3	3	3
Completed	0	2	2
Not completed	3	1	1
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Progressive disease	2	1	1
Protocol deviation	-	-	-

Number of subjects in period 1	L-DOS47 0.46 µg/kg_Phase I	L-DOS47 0.59 µg/kg_Phase I	L-DOS47 0.78 µg/kg_Phase I
Started	3	3	3
Completed	1	2	0
Not completed	2	1	3
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Progressive disease	2	1	3
Protocol deviation	-	-	-

Number of subjects in period 1	L-DOS47 1.04 µg/kg_Phase I	L-DOS47 1.38 µg/kg_Phase I	L-DOS47 1.84 µg/kg_Phase I
Started	3	4	3
Completed	0	1	3
Not completed	3	3	0
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	-
Progressive disease	3	2	-
Protocol deviation	-	-	-

Number of subjects in period 1	L-DOS47 2.45 µg/kg_Phase I	L-DOS47 3.26 µg/kg_Phase I	L-DOS47 4.33 µg/kg_Phase I
Started	5	4	3
Completed	1	1	1
Not completed	4	3	2
Adverse event, serious fatal	-	1	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	-
Progressive disease	2	1	1
Protocol deviation	-	1	-

Number of subjects in period 1	L-DOS47 5.76 µg/kg_Phase I	L-DOS47 7.66 µg/kg_Phase I	L-DOS47 10.19 µg/kg_Phase I
Started	6	3	3
Completed	4	0	1
Not completed	2	3	2
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	2	-	1
Progressive disease	-	2	1
Protocol deviation	-	-	-

Number of subjects in period 1	L-DOS47 13.55 µg/kg_Phase I	L-DOS47 13.55 µg/kg_Phase II
Started	3	21
Completed	3	6
Not completed	0	15
Adverse event, serious fatal	-	-
Consent withdrawn by subject	-	2
Adverse event, non-fatal	-	2
Progressive disease	-	11
Protocol deviation	-	-

Baseline characteristics

Reporting groups

Reporting group title	L-DOS47 0.12 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.21 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.33 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.46 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.59 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.78 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 1.04 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 1.38 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 1.84 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 2.45 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 3.26 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 4.33 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 5.76 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 7.66 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 10.19 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 13.55 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 13.55 µg/kg_Phase II

Reporting group description:

An initial 17 evaluable patients, based on Simon's optimal two-stage design, will be enrolled in the first stage. If ≥ 1 response, a further 22 patients would be enrolled in the second stage.

Reporting group values	L-DOS47 0.12 µg/kg_Phase I	L-DOS47 0.21 µg/kg_Phase I	L-DOS47 0.33 µg/kg_Phase I
Number of subjects	3	3	3
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.0	52.0	58.3
standard deviation	± 4.36	± 4.36	± 3.06
Gender categorical Units: Subjects			
Female	0	2	1
Male	3	1	2
Eastern Cooperative Oncology Group (ECOG) Performance Score Units: Subjects			
ECOG score=0	2	1	2
ECOG score=1	1	1	1
ECOG score =2	0	1	0
ECOG score=3	0	0	0
ECOG score=4	0	0	0

Reporting group values	L-DOS47 0.46 µg/kg_Phase I	L-DOS47 0.59 µg/kg_Phase I	L-DOS47 0.78 µg/kg_Phase I
Number of subjects	3	3	3
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	3
From 65-84 years	2	2	0
85 years and over	0	0	0

Age continuous Units: years			
arithmetic mean	71.0	70.0	61.0
standard deviation	± 10.44	± 11.53	± 2.00
Gender categorical Units: Subjects			
Female	1	1	2
Male	2	2	1
Eastern Cooperative Oncology Group (ECOG) Performance Score Units: Subjects			
ECOG score=0	1	0	1
ECOG score=1	2	3	2
ECOG score =2	0	0	0
ECOG score=3	0	0	0
ECOG score=4	0	0	0

Reporting group values	L-DOS47 1.04 µg/kg_Phase I	L-DOS47 1.38 µg/kg_Phase I	L-DOS47 1.84 µg/kg_Phase I
Number of subjects	3	4	3
Age categorical Units: Subjects			
Adults (18-64 years)	2	3	2
From 65-84 years	1	1	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	68.3	57.8	53.3
standard deviation	± 11.93	± 9.43	± 15.31
Gender categorical Units: Subjects			
Female	2	0	1
Male	1	4	2
Eastern Cooperative Oncology Group (ECOG) Performance Score Units: Subjects			
ECOG score=0	2	0	1
ECOG score=1	1	4	2
ECOG score =2	0	0	0
ECOG score=3	0	0	0
ECOG score=4	0	0	0

Reporting group values	L-DOS47 2.45 µg/kg_Phase I	L-DOS47 3.26 µg/kg_Phase I	L-DOS47 4.33 µg/kg_Phase I
Number of subjects	5	4	3
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	3
From 65-84 years	2	1	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.8	56.5	58.7

standard deviation	± 9.15	± 16.58	± 4.04

Gender categorical Units: Subjects			
Female	4	3	2
Male	1	1	1
Eastern Cooperative Oncology Group (ECOG) Performance Score Units: Subjects			
ECOG score=0	1	0	0
ECOG score=1	4	3	3
ECOG score =2	0	1	0
ECOG score=3	0	0	0
ECOG score=4	0	0	0

Reporting group values	L-DOS47 5.76 µg/kg_Phase I	L-DOS47 7.66 µg/kg_Phase I	L-DOS47 10.19 µg/kg_Phase I
Number of subjects	6	3	3
Age categorical Units: Subjects			
Adults (18-64 years)	4	2	1
From 65-84 years	2	1	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.0	57.3	64.3
standard deviation	± 12.21	± 12.22	± 3.06
Gender categorical Units: Subjects			
Female	2	1	3
Male	4	2	0
Eastern Cooperative Oncology Group (ECOG) Performance Score Units: Subjects			
ECOG score=0	1	1	0
ECOG score=1	5	2	3
ECOG score =2		0	
ECOG score=3		0	
ECOG score=4		0	

Reporting group values	L-DOS47 13.55 µg/kg_Phase I	L-DOS47 13.55 µg/kg_Phase II	Total
Number of subjects	3	21	76
Age categorical Units: Subjects			
Adults (18-64 years)	1	11	49
From 65-84 years	2	10	27
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	58.3	62.9	
standard deviation	± 15.01	± 7.66	-

Gender categorical Units: Subjects			
Female	1	10	36
Male	2	11	40
Eastern Cooperative Oncology Group (ECOG) Performance Score Units: Subjects			
ECOG score=0	1	2	16
ECOG score=1	2	18	57
ECOG score =2	0	1	3
ECOG score=3	0	0	0
ECOG score=4	0	0	0

Subject analysis sets

Subject analysis set title	Safety Population_Phase I
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Includes all patients who receive at least one dose of study drug.

Subject analysis set title	Safety Population_Phase II
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Includes all patients who receive at least one dose of study drug.

Subject analysis set title	Response Evaluable Population_Phase II
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Includes patients who have measurable disease at baseline, received at least one dose of study drug, and have at least one post-baseline response assessment.

Subject analysis set title	PP Population_Phase II
Subject analysis set type	Per protocol

Subject analysis set description:

Includes all patients who have completed ≥ 4 cycles of L-DOS47 treatment and have no major protocol violations.

Reporting group values	Safety Population_Phase I	Safety Population_Phase II	Response Evaluable Population_Phase II
Number of subjects	55	21	19
Age categorical Units: Subjects			
Adults (18-64 years)	38	11	9
From 65-84 years	17	10	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60.4	62.9	63.7
standard deviation	± 10.29	± 7.66	± 7.39
Gender categorical Units: Subjects			
Female	29	10	9
Male	26	11	10
Eastern Cooperative Oncology Group (ECOG) Performance Score Units: Subjects			

ECOG score=0	14	2	2
ECOG score=1	39	18	16
ECOG score =2	2	1	1
ECOG score=3	0	0	0
ECOG score=4	0	0	0

Reporting group values	PP Population_Phase II		
Number of subjects	5		
Age categorical Units: Subjects			
Adults (18-64 years)	1		
From 65-84 years	4		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	67.8		
standard deviation	± 4.06		
Gender categorical Units: Subjects			
Female	3		
Male	2		
Eastern Cooperative Oncology Group (ECOG) Performance Score Units: Subjects			
ECOG score=0	0		
ECOG score=1	5		
ECOG score =2	0		
ECOG score=3	0		
ECOG score=4	0		

End points

End points reporting groups

Reporting group title	L-DOS47 0.12 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.21 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.33 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.46 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.59 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 0.78 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 1.04 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 1.38 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 1.84 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 2.45 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 3.26 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 4.33 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 5.76 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 7.66 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 10.19 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 13.55 µg/kg_Phase I

Reporting group description:

Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort.

Reporting group title	L-DOS47 13.55 µg/kg_Phase II

Reporting group description:

An initial 17 evaluable patients, based on Simon's optimal two-stage design, will be enrolled in the first stage. If ≥ 1 response, a further 22 patients would be enrolled in the second stage.

Subject analysis set title	Safety Population_Phase I
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Includes all patients who receive at least one dose of study drug.

Subject analysis set title	Safety Population_Phase II
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Includes all patients who receive at least one dose of study drug.

Subject analysis set title	Response Evaluable Population_Phase II
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Includes patients who have measurable disease at baseline, received at least one dose of study drug, and have at least one post-baseline response assessment.

Subject analysis set title	PP Population_Phase II
Subject analysis set type	Per protocol

Subject analysis set description:

Includes all patients who have completed ≥ 4 cycles of L-DOS47 treatment and have no major protocol violations.

Primary: Incidence and severity of drug-related adverse events as per dose-limiting toxicity definition

End point title	Incidence and severity of drug-related adverse events as per dose-limiting toxicity definition[1][2]

End point description:

Dose-limiting toxicity was defined as any NCI CTCAE v.4.0 ≥ Grade 3 non-haematologic and any ≥ Grade 4 haematologic adverse event that is at least possibly related to the study drug occurring ≤ 3 weeks after commencing L-DOS47 treatment.

End point type	Primary

End point timeframe:

Observations period for dose-limiting toxicities was 21 days, the length of one complete treatment cycle.

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: No statistical analyses was required for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses was required for this endpoint.

End point values	L-DOS47 0.12 µg/kg_Phase I	L-DOS47 0.21 µg/kg_Phase I	L-DOS47 0.33 µg/kg_Phase I	L-DOS47 0.46 µg/kg_Phase I
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Number of patients	0	0	0	0

End point values	L-DOS47 0.59 µg/kg_Phase I	L-DOS47 0.78 µg/kg_Phase I	L-DOS47 1.04 µg/kg_Phase I	L-DOS47 1.38 µg/kg_Phase I
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Number of patients	0	0	0	0

End point values	L-DOS47 1.84 µg/kg_Phase I	L-DOS47 2.45 µg/kg_Phase I	L-DOS47 3.26 µg/kg_Phase I	L-DOS47 4.33 µg/kg_Phase I
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Number of patients	0	0	0	0

End point values	L-DOS47 5.76 µg/kg_Phase I	L-DOS47 7.66 µg/kg_Phase I	L-DOS47 10.19 µg/kg_Phase I	L-DOS47 13.55 µg/kg_Phase I
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	3	3
Units: Number of patients	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Overall response rate

End point title	Overall response rate[3]

End point description:

Proportion of patients with a best (confirmed) objective response (RECIST v1.1) of complete response (CR) or partial response (PR).

End point type	Primary

End point timeframe:

Overall response rate was evaluated at 6-week intervals from the start of the study treatment until PD or end of treatment period, whichever was earlier.

Notes:

[3] - 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: No statistical analyses was required for this endpoint.

End point values	Response Evaluable Population_Phase II			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Number of patients				
Complete response (CR) - confirmed	0			
Partial response (PR) - confirmed	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse events occurring or worsening (in terms of severity) or becoming serious between the first study drug intake date (included) and the last study drug intake date + 28 days (included).

Adverse event reporting additional description:

Disease progression was not reported as an adverse event, but death due to disease progression was captured as a serious adverse event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	0.12 µg/kg_Ph1
Reporting group description:	
All patients who received at least one dose of study drug.	
Reporting group title	0.21 µg/kg_Ph1
Reporting group description: -	
Reporting group title	0.33 µg/kg_Ph1
Reporting group description: -	
Reporting group title	0.46 µg/kg_Ph1
Reporting group description: -	
Reporting group title	0.59 µg/kg_Ph1
Reporting group description: -	
Reporting group title	0.78 µg/kg_Ph1
Reporting group description: -	
Reporting group title	1.04 µg/kg_Ph1
Reporting group description: -	
Reporting group title	1.38 µg/kg_Ph1
Reporting group description: -	
Reporting group title	1.84 µg/kg_Ph1
Reporting group description: -	
Reporting group title	2.45 µg/kg_Ph1
Reporting group description: -	
Reporting group title	3.26 µg/kg_Ph1
Reporting group description: -	
Reporting group title	4.33 µg/kg_Ph1
Reporting group description: -	
Reporting group title	5.76 µg/kg_Ph1
Reporting group description: -	
Reporting group title	7.66 µg/kg_Ph1
Reporting group description: -	
Reporting group title	10.19 µg/kg_Ph1
Reporting group description: -	
Reporting group title	13.55 µg/kg_Ph1
Reporting group description: -	
Reporting group title	All Patients_Ph I
Reporting group description: -	
Reporting group title	13.55 µg/kg_Ph2

Reporting group description: -

Serious adverse events	0.12 µg/kg_Ph1	0.21 µg/kg_Ph1	0.33 µg/kg_Ph1
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	0 / 3 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
ECOG performance status improvement			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contrast media reaction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (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
Humerus fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (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
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (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
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (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

Serious adverse events	0.46 µg/kg_Ph1	0.59 µg/kg_Ph1	0.78 µg/kg_Ph1
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 3 (66.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
ECOG performance status improvement			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contrast media reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	1.04 µg/kg_Ph1	1.38 µg/kg_Ph1	1.84 µg/kg_Ph1
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 4 (75.00%)	1 / 3 (33.33%)
number of deaths (all causes)	1	3	1
number of deaths resulting from adverse events	0	0	0
Investigations			
ECOG performance status improvement			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contrast media reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (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
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (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
Pleural effusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (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
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	2.45 µg/kg_Ph1	3.26 µg/kg_Ph1	4.33 µg/kg_Ph1
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	3 / 4 (75.00%)	1 / 3 (33.33%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0	0	0
Investigations			
ECOG performance status improvement			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (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
Non-small cell lung cancer			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contrast media reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (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
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (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
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (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

Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	5.76 µg/kg_Ph1	7.66 µg/kg_Ph1	10.19 µg/kg_Ph1
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	2 / 3 (66.67%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Investigations			
ECOG performance status improvement			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contrast media reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 3 (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
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	13.55 µg/kg_Ph1	All Patients_Ph I	13.55 µg/kg_Ph2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	22 / 55 (40.00%)	8 / 21 (38.10%)
number of deaths (all causes)	0	10	3
number of deaths resulting from adverse events	0	0	0
Investigations			
ECOG performance status improvement			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 3 (0.00%)	6 / 55 (10.91%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 6	0 / 2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contrast media reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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
Humerus fracture			

subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 55 (9.09%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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
General health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	2 / 55 (3.64%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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
Sudden death			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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

Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 3 (0.00%)	4 / 55 (7.27%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	2 / 55 (3.64%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 3 (0.00%)	4 / 55 (7.27%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	0 / 21 (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

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

Non-serious adverse events	0.12 µg/kg_Ph1	0.21 µg/kg_Ph1	0.33 µg/kg_Ph1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Astrocytoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Edema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Fatigue			

subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	4	0
General physical health deterioration			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Dyspnea			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Confusional state			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Myocardial ischemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Extrapyramidal disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0

Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhydrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	0.46 µg/kg_Ph1	0.59 µg/kg_Ph1	0.78 µg/kg_Ph1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Astrocytoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Edema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	3
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Dyspnea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			

Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Myocardial ischemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Extrapyramidal disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Diarrhea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhydrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2

Non-serious adverse events	1.04 µg/kg_Ph1	1.38 µg/kg_Ph1	1.84 µg/kg_Ph1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	3 / 4 (75.00%)	1 / 3 (33.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	1 / 3 (33.33%)
occurrences (all)	1	2	1
Astrocytoma			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Edema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnea			

subjects affected / exposed	2 / 3 (66.67%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Myocardial ischemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tachycardia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Extrapyramidal disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhydrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	2.45 µg/kg_Ph1	3.26 µg/kg_Ph1	4.33 µg/kg_Ph1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	4 / 4 (100.00%)	2 / 3 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Astrocytoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Edema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Disease progression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnea exertional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood albumin decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Myocardial ischemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Extrapyramidal disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	2	1	1

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhydrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	5.76 µg/kg_Ph1	7.66 µg/kg_Ph1	10.19 µg/kg_Ph1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	2 / 3 (66.67%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Astrocytoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Edema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			

subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	2	0	2
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Dyspnea			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnea exertional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Confusional state			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood albumin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Myocardial ischemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Extrapyramidal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	1	3
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Diarrhea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhydrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Non-serious adverse events	13.55 µg/kg_Ph1	All Patients_Ph I	13.55 µg/kg_Ph2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	44 / 55 (80.00%)	20 / 21 (95.24%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	0 / 3 (0.00%)	6 / 55 (10.91%)	4 / 21 (19.05%)
occurrences (all)	0	6	4
Astrocytoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	5 / 55 (9.09%)	2 / 21 (9.52%)
occurrences (all)	1	7	2
Edema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	3 / 55 (5.45%)	2 / 21 (9.52%)
occurrences (all)	0	3	2
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	8 / 55 (14.55%)	3 / 21 (14.29%)
occurrences (all)	0	12	3
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	4 / 55 (7.27%)	0 / 21 (0.00%)
occurrences (all)	0	4	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 55 (5.45%)	0 / 21 (0.00%)
occurrences (all)	0	3	0

Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	6 / 55 (10.91%)	1 / 21 (4.76%)
occurrences (all)	1	7	1
Dyspnea			
subjects affected / exposed	0 / 3 (0.00%)	15 / 55 (27.27%)	3 / 21 (14.29%)
occurrences (all)	0	15	3
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Dyspnea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	6 / 55 (10.91%)	0 / 21 (0.00%)
occurrences (all)	0	7	0
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Investigations			

Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 55 (3.64%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Cardiac disorders			
Myocardial ischemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Nervous system disorders			
Extrapyramidal disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 55 (9.09%)	1 / 21 (4.76%)
occurrences (all)	0	6	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	4 / 55 (7.27%)	1 / 21 (4.76%)
occurrences (all)	0	4	1
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 55 (3.64%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	8 / 55 (14.55%)	5 / 21 (23.81%)
occurrences (all)	0	11	7
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	5 / 55 (9.09%)	7 / 21 (33.33%)
occurrences (all)	0	6	12
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	1 / 21 (4.76%)
occurrences (all)	0	1	1

Diarrhea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 55 (3.64%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Hyperhydrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 55 (1.82%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 55 (5.45%)	2 / 21 (9.52%)
occurrences (all)	0	3	2
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 55 (5.45%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 55 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	5 / 55 (9.09%)	1 / 21 (4.76%)
occurrences (all)	0	6	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2011	First starting dose was decreased to 0.12 µg/kg. All male and female patients were mandated to use contraception during the study and for 3 months following completion of treatment. Addition of cytokine testing and recalculation of blood volume for safety testing.
12 September 2012	Non-substantial. Revision of committee name from Safety Review Committee (SRC) to Trial Steering Committee (TSC).
17 July 2013	Combination therapy arms were removed and L-DOS47 studied as monotherapy only.
18 October 2013	Change in Coordinating Investigator from Maciej Krzakowski, MD, PhD to Dariusz M. Kowalski, MD, PhD.
12 March 2014	Addition of dose levels in anticipation of dose expansion past 1.38 µg/kg and increase in patient numbers as a result. Revised criteria for Stable Disease (SD) assignment to align with RECIST v1.1. Further clarification of required radiological examinations.
16 December 2014	Addition of dose levels in anticipation of continued dose expansion past 4.33 µg/kg and increase in patient numbers as a result. Update to ongoing clinical study background information.
19 January 2016	For Phase II portion of the study, change in number of L-DOS47 administrations from 2 to 4 per cycle. Recalculation of the stopping rule for the Phase II interim analyses, based on the expected objective response rate for a monotherapy. The number of planned patients required for the Phase II interim analysis increased based on the new efficacy assumptions. Cohort 16 dose will be used in Phase II if MTD is not reached, provided TSC approves. Phase II Study Schedule added as Appendix 3. Addition of a new section summarizing Phase II assessments during L-DOS47 dosing. Clarification that serial blood samples for the measurement of cytokines collected for the Phase I study only.
16 May 2017	Sponsor office address change. End of Trial Visit (EOTV) completion defined in the Phase II component of the study, as well as limiting the number of additional cycles of L-DOS47 following a reassessment of the risk and potential benefit of L-DOS47 in the Phase II component of study LDOS002. Update to ongoing clinical studies background information. Update to the Benefit and Risk Assessment section of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Dose response ad hoc analysis not included in the summary of results.

Notes: