Clinical trial results:
A Phase 2, Multi-center, Randomized, Double-blind, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of ALD518 in the Reduction of Oral Mucositis in Subjects With Head and Neck Cancer Receiving Concomitant Chemotherapy and Radiotherapy

Summary

EudraCT number	2011-002669-40
Trial protocol	DE AT IT
Global end of trial date	25 September 2014

Results information

Result version number	v1 (current)
This version publication date	19 October 2022
First version publication date	19 October 2022
Summary attachment (see zip file)	ALD518-009 Clinical Trial Summary Report INS-717.547 (ALD518-009 CSR Synopsis Submission 28JUL2015.pdf)

Trial information

Trial identification

Sponsor protocol code	ALD518-CLIN-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01403064
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring
Sponsor organisation address	1020 First Avenue, King of Prussia, United States, 19406
Public contact	Study Director, CSL Behring, +1 610-878-4000 , clinicaltrials@cslbehring.com
Scientific contact	Study Director, CSL Behring, +1 610-878-4000 , clinicaltrials@cslbehring.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the clinical trial was to evaluate the safety and efficacy of ALD518 in modifying the course of oral mucositis (OM) in subjects with head and neck cancer (HNC) receiving concurrent chemotherapy and radiotherapy (CRT).

Protection of trial subjects:

Standard of care procedures were employed in order to minimize harm to the patients. Study staff continuously interacted with the patients and were thoroughly trained on patient rights as well as medically trained to handle any adverse events. Study staff were well-informed on procedures to handle subjects from pre-screening through the completion of the study. All patients were explained the alternatives to being a part of the study. Procedures were also in place to ensure there was no undue coercion during the informed consent process.

Background therapy:

Subjects were newly diagnosed with head and neck cancer and had not received previous treatment for oral mucositis. All enrolled subjects received a continuous course of conventional external beam irradiation delivered by intensity-modulated radiotherapy (IMRT) as single daily fractions of 2.0 to 2.2 Gy, with a cumulative radiation dose between 55 and 72 Gy at each site. Planned radiation treatment fields must include at least 2 oral sites (retromolar trigone, buccal mucosa, floor of mouth, tongue, or soft palate), with each site receiving ≥ 55 Gy. In addition to the experimental regimen (IMRT and ALD518 or IMRT and Placebo) randomized subjects also received a standard cisplatin or carboplatin CT regimen. Investigators were permitted to prescribe any concomitant medication or supportive therapy deemed necessary to provide adequate supportive care including antiemetics, systemic antibiotics, hydration to prevent renal damage, transfusions, topical fluoride, and saline rinses with the exceptions including Methotrexate, Nimesulide, Amifostine (Ethyol®), Antibiotic rinses and troches (antifungal rinses and troches are allowed for the treatment of candidiasis), Benzydamine hydrochloride, Caphosol, Cevimeline hydrochloride (Evoxac®), Glutamine as a prophylactic agent for mucositis, GM-CSF (e.g., Leukine®), IL-11 (Neumega®), 'Magic mouthwash', 'Miracle mouthwash' or other mouthwash solutions containing, Chlorhexidine, Hydrogen peroxide, or Diphenhydramine, Palifermin (Kepivance®) or other keratinocyte or fibroblast growth factor, Pilocarpine hydrochloride (Salagen®), Povidone-iodine rinses, Steroid rinses, Sucralfate in suspension form (use of sucralfate tablets is not proscribed), other biologic response modifiers – except hematopoietic growth factors for the management of anemia or myelosuppression and other investigational agents.

Evidence for comparator: -

Actual start date of recruitment	07 July 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 5

Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	76
EEA total number of subjects	34

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)	63
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 96 subjects were planned and 76 subjects were analyzed. 72 subjects entered long term follow up. The first subject, first visit occurred 29 August 2011 and the last subject, last visit occurred on 27 March 2014. This study was conducted at 20 study centers in Australia, Austria, Canada, Germany, Italy, and the USA.

Pre-assignment

Screening details:

Screening included adult subjects recently diagnosed with, pathologically confirmed, non-metastatic SCC of the oral cavity, oropharynx, hypopharynx or larynx and who had treatment plans for first-line CRT.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

0.9% saline administered as two intravenous infusions (IV) 3 weeks apart

Arm type	Placebo
Investigational medicinal product name	0.9% saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.9% saline administered as two intravenous infusions (IV) 3 weeks apart

Arm title	ALD518 (160 mg, OL)

Arm description:

ALD518 160 mg IV every 4 weeks for a total of 2 doses in open-label (OL) treatment

Arm type	Experimental
Investigational medicinal product name	ALD518
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ALD518 administered intravenously

Arm title	ALD518 (160 mg, R)

Arm description:

ALD518 160 mg IV every 3 weeks for a total of 2 doses in randomized (R) treatment

Arm type	Experimental

Investigational medicinal product name	0.9% saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.9% saline administered as two intravenous infusions (IV) 3 weeks apart

Arm title	ALD518 (320 mg, R)

Arm description:

ALD518 320 mg IV every 3 weeks for a total of 2 doses in randomized (R) treatment

Arm type	Experimental
Investigational medicinal product name	ALD518
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ALD518 administered intravenously

Number of subjects in period 1	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)
Started	24	7	23
Completed	23	7	19
Not completed	1	0	4
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	-	-	1
unknown	1	-	2

Number of subjects in period 1	ALD518 (320 mg, R)
Started	22
Completed	19
Not completed	3
Adverse event, serious fatal	1
Consent withdrawn by subject	1
unknown	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
0.9% saline administered as two intravenous infusions (IV) 3 weeks apart	
Reporting group title	ALD518 (160 mg, OL)
Reporting group description:	
ALD518 160 mg IV every 4 weeks for a total of 2 doses in open-label (OL) treatment	
Reporting group title	ALD518 (160 mg, R)
Reporting group description:	
ALD518 160 mg IV every 3 weeks for a total of 2 doses in randomized (R) treatment	
Reporting group title	ALD518 (320 mg, R)
Reporting group description:	
ALD518 320 mg IV every 3 weeks for a total of 2 doses in randomized (R) treatment	

Reporting group values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)
Number of subjects	24	7	23
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.8	56.3	58.6
standard deviation	± 7.92	± 11.93	± 7.43
Gender categorical Units: Subjects			
Female	4	1	7
Male	20	6	16

Reporting group values	ALD518 (320 mg, R)	Total	
Number of subjects	22	76	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	55.1		
standard deviation	± 7.18	-	
Gender categorical Units: Subjects			
Female	1	13	
Male	21	63	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
0.9% saline administered as two intravenous infusions (IV) 3 weeks apart	
Reporting group title	ALD518 (160 mg, OL)
Reporting group description:	
ALD518 160 mg IV every 4 weeks for a total of 2 doses in open-label (OL) treatment	
Reporting group title	ALD518 (160 mg, R)
Reporting group description:	
ALD518 160 mg IV every 3 weeks for a total of 2 doses in randomized (R) treatment	
Reporting group title	ALD518 (320 mg, R)
Reporting group description:	
ALD518 320 mg IV every 3 weeks for a total of 2 doses in randomized (R) treatment	

Primary: Number of Participants With All Grades of OM at a Radiation Dose of 55 Gy

End point title	Number of Participants With All Grades of OM at a Radiation Dose of 55 Gy[1]
End point description:	
The 55 Gy ulcerative OM assessment is defined as the first ulcerative OM assessment that occurred on the day of or after the subject received the radiation therapy that first resulted in their cumulative dose of radiation being ≥ 55 Gy	
End point type	Primary
End point timeframe:	
Up to 12 weeks	

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: Descriptive statistics were used.

End point values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)	ALD518 (320 mg, R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	7	23	22
Units: Participants				
number (not applicable)	19	5	23	17

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Ulcerative OM at Varying Cumulative Radiation Doses (Gy)

End point title	Number of Participants With Ulcerative OM at Varying Cumulative Radiation Doses (Gy)
End point description:	
The ulcerative OM assessment at a specific cumulative radiation dose (35 Gy, 45 Gy, 55 Gy or 65 Gy) is	

defined as the first ulcerative OM assessment that occurred on the day of or after the subject received the radiation therapy that first resulted in the specific cumulative dose of radiation being ≥35 Gy, ≥45 Gy, ≥55 Gy or≥ 65 Gy

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)	ALD518 (320 mg, R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24[2]	7[3]	22[4]	20[5]
Units: Participants				
number (not applicable)				
35 Gy	14	6	18	13
45 Gy	21	6	20	15
55 Gy	19	5	22	15
65 Gy	15	5	19	11

Notes:

[2] - For 35, 45, 55, and 65 Gy, n = 24, 24, 24 and 18, respectively

[3] - For 35, 45, 55, and 65 Gy, n = 7, 7, 7 and 6, respectively

[4] - For 35, 45, 55, and 65 Gy, n = 22, 22, 22 and 19, respectively

[5] - For 35, 45, 55, and 65 Gy, n = 20, 20, 20 and 16, respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Severe OM at Varying Cumulative Radiation Doses (Gy)

End point title	Number of Participants With Severe OM at Varying Cumulative Radiation Doses (Gy)

End point description:

The severe OM assessment at a specific cumulative radiation dose (35 Gy, 45 Gy, 55 Gy or 65 Gy) is defined as the first severe OM assessment that occurred on the day of or after the subject received the radiation therapy that first resulted in the specific cumulative dose of radiation being ≥35 Gy, ≥45 Gy, ≥55 Gy or≥ 65 Gy

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)	ALD518 (320 mg, R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24[6]	7[7]	22[8]	20[9]
Units: Participants				
number (not applicable)				
35 Gy	6	4	6	6
45 Gy	10	5	8	9
55 Gy	12	5	9	11

65 Gy	10	3	12	7

Notes:

[6] - For 35, 45, 55, and 65 Gy, n = 24, 24, 24 and 18, respectively

[7] - For 35, 45, 55, and 65 Gy, n = 7, 7, 7 and 6, respectively

[8] - For 35, 45, 55, and 65 Gy, n = 22, 22, 22 and 19, respectively

[9] - For 35, 45, 55, and 65 Gy, n = 20, 20, 20 and 16, respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Ulcerative and Severe OM

End point title	Duration of Ulcerative and Severe OM

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)	ALD518 (320 mg, R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	7	23	22
Units: Days				
arithmetic mean (standard deviation)				
Ulcerative	42.0 (± 23.17)	55.1 (± 26.57)	48.3 (± 16.71)	38.0 (± 29.53)
Severe	22.4 (± 23.28)	35.1 (± 28.02)	22.7 (± 18.95)	21.5 (± 25.01)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Ulcerative and Severe OM

End point title	Time to Onset of Ulcerative and Severe OM

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)	ALD518 (320 mg, R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24[10]	7[11]	23[12]	22[13]
Units: Days				
arithmetic mean (standard deviation)				
Ulcerative	23.7 (± 7.05)	18.7 (± 5.32)	22.9 (± 5.97)	24.3 (± 13.37)
Severe	37.0 (± 11.81)	26.1 (± 5.72)	43.1 (± 17.55)	38.0 (± 15.64)

Notes:

[10] - For ulcerative and severe OM, n = 22 and 15, respectively

[11] - For ulcerative and severe OM, n = 6 and 5, respectively

[12] - For ulcerative and severe OM, n = 22 and 20, respectively

[13] - For ulcerative and severe OM, n = 18 and 14, respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Oral Mucositis Daily Questionnaire (OMDQ) Overall Health Score at Varying Cumulative Radiation Doses (Gy)

End point title	Oral Mucositis Daily Questionnaire (OMDQ) Overall Health Score at Varying Cumulative Radiation Doses (Gy)

End point description:

Scored on a scale from 0 (worst possible overall health) to 10 (perfect overall health). Higher scores represent better overall health.

End point type	Secondary

End point timeframe:

Baseline and up to 12 weeks

End point values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)	ALD518 (320 mg, R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24[14]	7[15]	23[16]	22[17]
Units: Score				
arithmetic mean (standard deviation)				
Baseline	6.5 (± 1.95)	8.4 (± 1.40)	7.2 (± 1.66)	6.7 (± 2.35)
35 Gy (up to 12 weeks)	5.2 (± 2.08)	6.6 (± 2.07)	5.2 (± 2.05)	5.5 (± 1.91)
45 Gy (up to 12 weeks)	5.6 (± 1.89)	5.7 (± 2.14)	5.4 (± 1.86)	5.4 (± 2.40)
55 Gy (up to 12 weeks)	5.1 (± 1.96)	5.9 (± 2.54)	5.3 (± 2.22)	5.1 (± 2.27)
65 Gy (up to 12 weeks)	5.6 (± 1.79)	5.7 (± 3.08)	5.3 (± 2.11)	5.6 (± 2.37)

Notes:

[14] - For baseline, 35, 45, 55, and 65 Gy, n = 22, 24, 24, 22, and 18, respectively

[15] - For baseline, 35, 45, 55, and 65 Gy, n = 7, 7, 7, 7, and 6, respectively

[16] - For baseline, 35, 45, 55, and 65 Gy, n = 20, 22, 21, 21, and 16, respectively

[17] - For baseline, 35, 45, 55, and 65 Gy, n = 18, 20, 17, 18, and 14, respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy - Head and Neck (FACT-HN)

Questionnaire Overall Assessment Score at Varying Cumulative Radiation Doses (Gy)

End point title	Functional Assessment of Cancer Therapy - Head and Neck (FACT-HN) Questionnaire Overall Assessment Score at Varying Cumulative Radiation Doses (Gy)

End point description:

The FACT-HN consists of 28 general + 11 head and neck specific items, each rated on a 0 (not at all) to 4 (very much) Likert type scale. The total score ranges from 0 to 148. Higher scores represent better quality of life.

End point type	Secondary

End point timeframe:

Baseline and up to 12 weeks

End point values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)	ALD518 (320 mg, R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24[18]	7[19]	23[20]	22[21]
Units: Score				
arithmetic mean (standard deviation)				
Baseline	116.5 (± 15.86)	129.4 (± 12.63)	113.8 (± 19.53)	111.3 (± 20.94)
35 Gy (up to 12 weeks)	92.9 (± 20.14)	100.3 (± 24.14)	96.2 (± 21.18)	92.2 (± 19.96)
45 Gy (up to 12 weeks)	90.6 (± 18.18)	94.7 (± 30.14)	89.7 (± 23.49)	86.6 (± 21.34)
55 Gy (up to 12 weeks)	89.6 (± 19.36)	82.3 (± 17.79)	84.4 (± 25.67)	81.1 (± 22.13)
65 Gy (up to 12 weeks)	85.2 (± 18.13)	93.6 (± 27.50)	86.5 (± 18.00)	86.5 (± 23.95)

Notes:

[18] - For baseline, 35, 45, 55, and 65 Gy, n = 22, 23, 24, 24, and 18, respectively

[19] - For baseline, 35, 45, 55, and 65 Gy, n = 7, 7, 7, 6, and 6, respectively

[20] - For baseline, 35, 45, 55, and 65 Gy, n = 22, 22, 20, 19, and 19, respectively

[21] - For baseline, 35, 45, 55, and 65 Gy, n = 20, 20, 19, 19, and 16, respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Chronic Illness Therapy - Fatigue Questionnaire (FACIT-F) Score at Varying Cumulative Radiation Doses (Gy)

End point title	Functional Assessment of Chronic Illness Therapy - Fatigue Questionnaire (FACIT-F) Score at Varying Cumulative Radiation Doses (Gy)

End point description:

The responses to the 13 items on the FACIT-F questionnaire are each measured on a 5-point Likert scale from 0 (not at all fatigued) to 4 (very much fatigued). The total score ranges from 0 to 52. Higher scores represent more fatigue.

End point type	Secondary

End point timeframe:

Baseline and up to 12 weeks

End point values	Placebo	ALD518 (160 mg, OL)	ALD518 (160 mg, R)	ALD518 (320 mg, R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24[22]	7[23]	23[24]	22[25]
Units: Score				
arithmetic mean (standard deviation)				
Baseline	42.5 (± 7.26)	47.6 (± 3.26)	42.6 (± 8.61)	39.7 (± 10.94)
35 Gy (up to 12 weeks)	31.1 (± 12.56)	30.1 (± 16.63)	34.0 (± 9.59)	31.2 (± 13.56)
45 Gy (up to 12 weeks)	30.3 (± 11.42)	28.9 (± 15.61)	31.2 (± 12.33)	30.4 (± 11.65)
55 Gy (up to 12 weeks)	29.9 (± 12.95)	20.8 (± 14.70)	28.0 (± 12.95)	26.8 (± 13.71)
65 Gy (up to 12 weeks)	29.6 (± 10.81)	26.8 (± 18.71)	27.3 (± 9.65)	29.5 (± 12.40)

Notes:

[22] - For baseline, 35, 45, 55, and 65 Gy, n = 24, 22, 24, 24, and 18, respectively

[23] - For baseline, 35, 45, 55, and 65 Gy, n = 7, 7, 7, 6, and 6, respectively

[24] - For baseline, 35, 45, 55, and 65 Gy, n = 23, 22, 20, 20, and 19, respectively

[25] - For baseline, 35, 45, 55, and 65 Gy, n = 21, 20, 19, 19, and 16, respectively

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 15 months for each participant

Adverse event reporting additional description:

Safety Population defined as any subject who received at least 1 dose of ALD518 or placebo. Subjects were analyzed based on the treatment they received. As pre-specified, the two treatment groups that received 160 mg were combined into one 160 mg group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

0.9% saline administered as two intravenous infusions (IV) 3 weeks apart

Reporting group title	ALD518 (160 mg)

Reporting group description:

ALD518 160 mg IV every 4 weeks for a total of 2 doses in open-label (OL) treatment or ALD518 160 mg IV every 3 weeks for a total of 2 doses in randomized (R) treatment.

Reporting group title	ALD518 (320 mg)

Reporting group description:

ALD518 320 mg IV every 3 weeks for a total of 2 doses in randomized (R) treatment

Serious adverse events	Placebo	ALD518 (160 mg)	ALD518 (320 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 23 (30.43%)	15 / 32 (46.88%)	8 / 21 (38.10%)
number of deaths (all causes)	0	4	2
number of deaths resulting from adverse events	0	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 23 (4.35%)	3 / 32 (9.38%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Obstructive airway disorder			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Tracheal fistula			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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 phosphorous decreased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Troponin increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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
Tracheostomy malfunction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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 / 1
Atrial fibrillation			

subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Coronary artery disease			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Myocardial infarction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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
Pancytopenia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Ear and labyrinth disorders			
Tinnitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Gastrointestinal disorders			
Dysphagia			

subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (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
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	3 / 32 (9.38%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral pain			
subjects affected / exposed	1 / 23 (4.35%)	2 / 32 (6.25%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Tongue haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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
Vomiting			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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 impairment			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Infections and infestations			

Abscess limb			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (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
Bacteraemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Lower respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Pneumonia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 23 (8.70%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	ALD518 (160 mg)	ALD518 (320 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 23 (95.65%)	32 / 32 (100.00%)	21 / 21 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			

subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Tumour ulceration			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Aortic dilatation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Deep vein thrombosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 23 (4.35%)	2 / 32 (6.25%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Hypotension			
subjects affected / exposed	2 / 23 (8.70%)	2 / 32 (6.25%)	2 / 21 (9.52%)
occurrences (all)	2	2	2
Lymphoedema			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Orthostatic hypotension			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 23 (13.04%)	4 / 32 (12.50%)	4 / 21 (19.05%)
occurrences (all)	3	4	4
Catheter site haemorrhage			

subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Catheter site inflammation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Catheter site oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Catheter site pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Drug intolerance			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Face oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	8 / 23 (34.78%)	7 / 32 (21.88%)	5 / 21 (23.81%)
occurrences (all)	8	7	5
Hyperthermia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Infusion site erythema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Local swelling			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Localized oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Malaise			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			

subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Pyrexia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 23 (8.70%)	3 / 32 (9.38%)	7 / 21 (33.33%)
occurrences (all)	2	3	7
Dysphonia			
subjects affected / exposed	3 / 23 (13.04%)	3 / 32 (9.38%)	3 / 21 (14.29%)
occurrences (all)	3	3	3
Dyspnoea			
subjects affected / exposed	1 / 23 (4.35%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Epiglottic oedema			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Haemoptysis			
subjects affected / exposed	0 / 23 (0.00%)	4 / 32 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	4	1
Hiccups			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Hypoxia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Increased upper airway secretion			
subjects affected / exposed	4 / 23 (17.39%)	4 / 32 (12.50%)	1 / 21 (4.76%)
occurrences (all)	4	4	1
Laryngeal oedema			

subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	4 / 23 (17.39%)	8 / 32 (25.00%)	6 / 21 (28.57%)
occurrences (all)	4	8	6
Pleuritic pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Sputum discolored			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Sputum increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Anxiety			
subjects affected / exposed	1 / 23 (4.35%)	4 / 32 (12.50%)	4 / 21 (19.05%)
occurrences (all)	1	4	4
Confusional state			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Depressed mood			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 23 (4.35%)	4 / 32 (12.50%)	1 / 21 (4.76%)
occurrences (all)	1	4	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 23 (8.70%)	2 / 32 (6.25%)	3 / 21 (14.29%)
occurrences (all)	2	2	3
Blood alkaline phosphotase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Blood bicarbonate decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood calcium decreased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood chloride decreased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 23 (0.00%)	3 / 32 (9.38%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Blood creatinine increased			
subjects affected / exposed	1 / 23 (4.35%)	5 / 32 (15.63%)	1 / 21 (4.76%)
occurrences (all)	1	5	1
Blood glucose increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Blood potassium decreased			
subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Blood pressure diastolic increased			

subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood triglycerides increased			
subjects affected / exposed	0 / 23 (0.00%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Blood urea increased			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
C-reactive protein increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram change			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Globulins decreased			
subjects affected / exposed	0 / 23 (0.00%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Haematocrit decreased			
subjects affected / exposed	2 / 23 (8.70%)	1 / 32 (3.13%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Haemoglobin decreased			
subjects affected / exposed	2 / 23 (8.70%)	3 / 32 (9.38%)	2 / 21 (9.52%)
occurrences (all)	2	3	2

Lymphocyte count decreased			
subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	2
Mean cell haemoglobin concentration decreased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Mean cell haemoglobin decreased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Mean cell volume decreased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Neutrophil count decreased			
subjects affected / exposed	2 / 23 (8.70%)	2 / 32 (6.25%)	6 / 21 (28.57%)
occurrences (all)	2	2	6
Platelet count decreased			
subjects affected / exposed	2 / 23 (8.70%)	7 / 32 (21.88%)	8 / 21 (38.10%)
occurrences (all)	2	7	8
Prealbumin decreased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Red blood cell count decreased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Renal function test abnormal			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Reticulocyte count decreased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	7 / 23 (30.43%)	11 / 32 (34.38%)	11 / 21 (52.38%)
occurrences (all)	7	11	11
White blood cell count decreased			

subjects affected / exposed	2 / 23 (8.70%)	3 / 32 (9.38%)	9 / 21 (42.86%)
occurrences (all)	2	3	9
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Post procedural haematoma			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Post procedural oedema			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Radiation fibrosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Radiation skin injury			
subjects affected / exposed	7 / 23 (30.43%)	8 / 32 (25.00%)	5 / 21 (23.81%)
occurrences (all)	7	8	5
Suture related complication			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Tracheal obstruction			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Bundle branch block left			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Nervous system disorders			

Ageusia			
subjects affected / exposed	1 / 23 (4.35%)	3 / 32 (9.38%)	2 / 21 (9.52%)
occurrences (all)	1	3	2
Aphasia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Aphonia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cognitive disorder			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 23 (4.35%)	7 / 32 (21.88%)	1 / 21 (4.76%)
occurrences (all)	1	7	1
Drooling			
subjects affected / exposed	1 / 23 (4.35%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Dysgeusia			
subjects affected / exposed	12 / 23 (52.17%)	11 / 32 (34.38%)	5 / 21 (23.81%)
occurrences (all)	12	11	5
Headache			
subjects affected / exposed	8 / 23 (34.78%)	6 / 32 (18.75%)	3 / 21 (14.29%)
occurrences (all)	8	6	3
Hypogeusia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Myoclonus			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Polyneuropathy			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Tongue biting			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Tongue paralysis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Drug dependence			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	4 / 23 (17.39%)	6 / 32 (18.75%)	1 / 21 (4.76%)
occurrences (all)	4	6	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 23 (17.39%)	10 / 32 (31.25%)	4 / 21 (19.05%)
occurrences (all)	4	10	4
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Erythropenia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Leukopenia			
subjects affected / exposed	7 / 23 (30.43%)	13 / 32 (40.63%)	6 / 21 (28.57%)
occurrences (all)	7	13	6
Lymphadenopathy			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Lymphatic obstruction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Lymphopenia			

subjects affected / exposed	2 / 23 (8.70%)	3 / 32 (9.38%)	2 / 21 (9.52%)
occurrences (all)	2	3	2
Neutropenia			
subjects affected / exposed	3 / 23 (13.04%)	10 / 32 (31.25%)	5 / 21 (23.81%)
occurrences (all)	3	10	5
Pancytopenia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	2 / 23 (8.70%)	9 / 32 (28.13%)	7 / 21 (33.33%)
occurrences (all)	2	9	7
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Ear discomfort			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Ear pain			
subjects affected / exposed	1 / 23 (4.35%)	5 / 32 (15.63%)	3 / 21 (14.29%)
occurrences (all)	1	5	3
Hyperacusis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hypoacusis			
subjects affected / exposed	2 / 23 (8.70%)	2 / 32 (6.25%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Tinnitis			
subjects affected / exposed	4 / 23 (17.39%)	2 / 32 (6.25%)	2 / 21 (9.52%)
occurrences (all)	4	2	2
Vertigo			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Periorbital oedema			

subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 23 (0.00%)	3 / 32 (9.38%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Abdominal pain upper			
subjects affected / exposed	2 / 23 (8.70%)	2 / 32 (6.25%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Aphagia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Breath odor			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Constipation			
subjects affected / exposed	13 / 23 (56.52%)	22 / 32 (68.75%)	9 / 21 (42.86%)
occurrences (all)	13	22	9
Diarrhoea			
subjects affected / exposed	10 / 23 (43.48%)	7 / 32 (21.88%)	3 / 21 (14.29%)
occurrences (all)	10	7	3
Dry mouth			
subjects affected / exposed	10 / 23 (43.48%)	11 / 32 (34.38%)	5 / 21 (23.81%)
occurrences (all)	10	11	5
Dyspepsia			
subjects affected / exposed	3 / 23 (13.04%)	4 / 32 (12.50%)	1 / 21 (4.76%)
occurrences (all)	3	4	1
Dysphagia			
subjects affected / exposed	6 / 23 (26.09%)	12 / 32 (37.50%)	2 / 21 (9.52%)
occurrences (all)	6	12	2
Epigastric discomfort			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 23 (4.35%)	5 / 32 (15.63%)	2 / 21 (9.52%)
occurrences (all)	1	5	2
Glossitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Glossodynia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	3 / 21 (14.29%)
occurrences (all)	0	1	3
Haemorrhoids			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Mouth ulceration			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	14 / 23 (60.87%)	20 / 32 (62.50%)	14 / 21 (66.67%)
occurrences (all)	14	20	14
Odynophagia			
subjects affected / exposed	5 / 23 (21.74%)	5 / 32 (15.63%)	4 / 21 (19.05%)
occurrences (all)	5	5	4
Oral mucosal erythema			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	9 / 23 (39.13%)	3 / 32 (9.38%)	7 / 21 (33.33%)
occurrences (all)	9	3	7
Regurgitation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Saliva altered			
subjects affected / exposed	1 / 23 (4.35%)	2 / 32 (6.25%)	2 / 21 (9.52%)
occurrences (all)	1	2	2
Salivary hypersecretion			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	2 / 21 (9.52%)
occurrences (all)	0	1	2

Stomatitis			
subjects affected / exposed	2 / 23 (8.70%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Swollen tongue			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Tongue oedema			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Tongue ulceration			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	9 / 23 (39.13%)	12 / 32 (37.50%)	10 / 21 (47.62%)
occurrences (all)	9	12	10
Hepatobiliary disorders			
Hyperbilirubinemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	3 / 23 (13.04%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	2	2	1
Ecchymosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	2 / 23 (8.70%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	2	2	1
Hyperhidrosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Photodermatosis			

subjects affected / exposed	1 / 23 (4.35%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Pruritis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Psoriasis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 23 (0.00%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Rash macular			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Skin discoloration			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nocturia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Oliguria			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Polyuria			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Proteinuria			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Urinary retention			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Muscle twitching			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	2 / 23 (8.70%)	2 / 32 (6.25%)	1 / 21 (4.76%)
occurrences (all)	2	2	1
Pain in extremity			

subjects affected / exposed	1 / 23 (4.35%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Pain in jaw			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Diverticulitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Erysipelas			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Febrile infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Herpes simplex			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Infective glossitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection fungal			

subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	4 / 23 (17.39%)	1 / 32 (3.13%)	3 / 21 (14.29%)
occurrences (all)	4	1	3
Oral candidiasis			
subjects affected / exposed	11 / 23 (47.83%)	18 / 32 (56.25%)	8 / 21 (38.10%)
occurrences (all)	11	18	8
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 23 (0.00%)	2 / 32 (6.25%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Post procedural cellulitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pseudomonas infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Staphylococcal pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Tinea cruris			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Tracheostomy infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			

subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	2 / 32 (6.25%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Viral infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 23 (21.74%)	4 / 32 (12.50%)	1 / 21 (4.76%)
occurrences (all)	5	4	1
Dehydration			
subjects affected / exposed	1 / 23 (4.35%)	5 / 32 (15.63%)	1 / 21 (4.76%)
occurrences (all)	1	5	1
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Electrolyte imbalance			
subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Gout			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Hypernatraemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Hypertriglyceridaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 32 (3.13%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	1 / 23 (4.35%)	2 / 32 (6.25%)	4 / 21 (19.05%)
occurrences (all)	1	2	4
Hypokalaemia			
subjects affected / exposed	0 / 23 (0.00%)	5 / 32 (15.63%)	4 / 21 (19.05%)
occurrences (all)	0	5	4
Hypomagnesaemia			
subjects affected / exposed	1 / 23 (4.35%)	2 / 32 (6.25%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Hyponatraemia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 32 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Hypophagia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 32 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2012	•Updated to indicate that the DMC approved the addition of 4 subjects in the open-label phase of the study and changed dosing schedule from every 4 weeks to every 3 weeks. •For inclusion criteria (IC) #3, clarified regions of radiation treatment and added "retromolar trigone". •In IC #4, removed details for chemo regimens; sites instructed to use their standard of care. •Changed day of first dose of ALD518 to Day 0 from Day 1. •Removed RECIST criteria and replaced with standard TNM criteria. •Added Canada to list of countries participating. •Added Cockcroft-Gault calculation for renal function in IC #7. •Revised IC #8 to state that subjects cannot be currently breastfeeding. •Revised exclusion criteria (EC) #10 to include previous exposure to active TB or histoplasmosis infection, in addition to previous history. •Deleted EC #12 and EC #18 •Added EC #19 - to exclude subjects who have a history of diverticulosis, diverticulitis, perforated diverticular diseases, or small bowel and/or upper GI perforation •Updated likely duration of clinical trial participation to 16 months from 15 months. •Added death to primary safety endpoints. •Clarified the upper transaminase level criteria in the Criteria for Discontinuation of Investigational Product. •Lab safety tests changed from collection every 3-4 weeks during RT to collection every week during RT. •Plasma IL-6 changed to Serum IL-6 •2 additional PK and immunogenicity timepoints added –Visits 8 and 14 – due to dosing schedule change. •Clarification added to continue OM assessments of subjects who have OM at week 4 post-RT •Clarification stating that Visit 18 should always be the last day of radiation therapy. •Added new figures to show the PK modeling for 3 week dosing and to compare 3 week to 4 week dosing. •Updated vital sign schedule new ALD518 infusion schedule. •Added updates regarding SAE reporting contact info. •Clarified that screen-failed population will not be statistically analysed.
27 November 2012	•Revised exclusion criteria #1 to exclude subjects who have tumor invasion of major vessels. •Germany and Canada were the only countries to request this amendment. The Nov 2012 administrative letter (below) was acceptable in all other countries. Administrative Letter 09 Nov 2012 •Revised exclusion criteria #1 to exclude subjects who have tumor invasion of major vessels.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported