



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 standard deviation | 58.8 ± 7.92 | 56.3 ± 11.93 | 58.6 ± 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 standard deviation | 55.1 ± 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 \geq 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 | | | |
| Tinnitus | | | |
| 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 phosphatase 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 occurrences (all) | 2 / 23 (8.70%) 2 | 3 / 32 (9.38%) 3 | 9 / 21 (42.86%) 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 occurrences (all) | 0 / 23 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Tongue paralysis subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Depression subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 0 |
| Drug dependence subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 23 (17.39%) 4 | 6 / 32 (18.75%) 6 | 1 / 21 (4.76%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 4 / 23 (17.39%) 4 | 10 / 32 (31.25%) 10 | 4 / 21 (19.05%) 4 |
| Disseminated intravascular coagulation subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 0 |
| Erythropenia subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 0 |
| Leukopenia subjects affected / exposed occurrences (all) | 7 / 23 (30.43%) 7 | 13 / 32 (40.63%) 13 | 6 / 21 (28.57%) 6 |
| Lymphadenopathy subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 0 / 32 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Lymphatic obstruction subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Lymphopenia | | | |

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

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 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 |

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|----------------------------------|------------------|------------------|------------------|
| 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 occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 0 |
| Renal failure subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 0 |
| Urinary retention subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 32 (3.13%) 1 | 1 / 21 (4.76%) 1 |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 0 / 32 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Muscle twitching subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 0 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Musculoskeletal discomfort subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 32 (3.13%) 1 | 0 / 21 (0.00%) 0 |
| Myalgia subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 0 / 32 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Neck pain subjects affected / exposed occurrences (all) | 2 / 23 (8.70%) 2 | 2 / 32 (6.25%) 2 | 1 / 21 (4.76%) 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 | <ul style="list-style-type: none">•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 | <ul style="list-style-type: none">•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. <p>Administrative Letter 09 Nov 2012</p> <ul style="list-style-type: none">•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