



Clinical trial results:

Phase 1/2 Study of anti-PD-L1 in Combination with Chemo(radio)therapy for Oesophageal Cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-005298-19 |
| Trial protocol | GB |
| Global end of trial date | 17 June 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 15 December 2022 |
| First version publication date | 15 December 2022 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | LUD2015-005 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02735239 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Ludwig Institute for Cancer Research Ltd |
| Sponsor organisation address | 600 3rd Avenue 32nd Floor, New York, United States, 10016 |
| Public contact | Jonathan Skipper, Ludwig Institute for Cancer Research Ltd, 001 2124501539, jskipper@lcr.org |
| Scientific contact | Jonathan Skipper, Ludwig Institute for Cancer Research Ltd, 001 2124501539, jskipper@lcr.org |

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 | 28 July 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 June 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 June 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objectives are (1) to assess the safety and tolerability of durvalumab alone and tremelimumab + durvalumab in combination with oxaliplatin/capecitabine chemotherapy in metastatic or locally advanced oesophageal cancer (OC), and then (2) to assess the safety and tolerability of durvalumab in combination with neoadjuvant chemo(radio)therapy before surgery in operable oesophageal cancer. Secondary objectives are (1) to assess the clinical efficacy of durvalumab alone and tremelimumab + durvalumab in combination with oxaliplatin/capecitabine chemotherapy in metastatic or locally advanced OC. (Endpoints: Tumor Response by irRECIST, progression-free survival [PFS] and overall survival [OS]) and (2) to assess the clinical efficacy of durvalumab in combination with neoadjuvant chemo(radio)therapy (oxaliplatin/capecitabine, FLOT, and paclitaxel/carboplatin/radiotherapy) in operable OC. (Endpoints: PFS after surgery, 1-year survival rate, OS, response rate)

Protection of trial subjects:

Subjects were given full and adequate written information about the nature, purpose and possible risks and benefits of the study. Dose adjustments, delays and discontinuation criteria were included in the protocol in the form of dose adjustment and management guidelines for toxicity related to study treatment.

Phase 1 of the study (Cohorts A1 and A2) evaluated the feasibility/safety of administering durvalumab or tremelimumab + durvalumab pre-operatively to OC subjects. Once safety was established in these cohorts, the additional cohorts were open for enrollment.

In addition, safety monitoring and study stopping rules were implemented in the protocol.

The assessment of safety and tolerability was performed by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the investigators.

Standard safety evaluation and reporting for early phase trials were used for Cohorts B, C/C-FLOT, and D/D2. In addition, for Cohorts C/C-FLOT and D/D2, subjects undergoing surgery were closely monitored for post-operative complications to evaluate the possibility of an impact.

Laboratory tests, vital sign measurements, physical exams (including neurological exams) and subject interviews were performed to detect new abnormalities and deteriorations of any pre-existing conditions. The investigator evaluated any laboratory abnormalities for clinical significance, and clinically significant abnormalities were recorded as adverse events. All clinically significant abnormalities and deteriorations from time of signing of informed consent to the end of study visit were to be recorded in the Case Report Forms as adverse events and graded according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE), version 4.03.

Background therapy:

The fluoropyrimidine-platinum (traditionally 5FU-cisplatin) based CRT regimen has long been a standard of care in the pre-operative management of oesophageal cancer. The use of this combination was largely historic, with only one small positive trial, and several meta-analyses supporting its use over surgery alone. The oxaliplatin-capecitabine based CRT regimen was selected over the cisplatin-fluoropyrimidine regime for Cohorts A, B & C based on several factors including maintaining the same chemotherapy backbone in the metastatic or locally advanced OC Cohorts A & B as in the Cohort C neoadjuvant chemotherapy arm of the trial. This decision was based on a randomized Phase 2 study in definitive chemoradiation showing comparable efficacy and less toxicity of oxaliplatin-5FU combination in comparison to cisplatin-5FU combination, emerging Phase 1b/2 data suggesting feasibility and activity of oxaliplatin-fluoropyrimidine based CRT regimens in the pre-operative setting and use of this regimen in the NEOSCOPE trial, a randomized Phase 2 trial that was ongoing in the UK at the time when this protocol was being developed.

While the trial was ongoing, two additional background treatments were added for subjects with operable OC based on emerging data.

In Cohort C-FLOT, oxaliplatin and capecitabine as neoadjuvant chemotherapy was replaced with the FLOT regimen to run concurrently with durvalumab treatment, and introducing post-operative chemotherapy, also with FLOT. This was to run concurrently with durvalumab immunotherapy.

In Cohort D, 2 doses of durvalumab were to be given during a 4-week immunotherapy period, followed by neoadjuvant chemoradiotherapy (5 weekly doses of paclitaxel + carboplatin + radiotherapy) without concurrent durvalumab. Cohort D2 is a subset of Cohort D subjects for whom durvalumab doses were to continue during chemoradiotherapy, after the initial 4-week immunotherapy.

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 22 April 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 73 |
| Worldwide total number of subjects | 73 |
| EEA total number of subjects | 0 |

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) | 47 |
| From 65 to 84 years | 26 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment was from 22 April 2016 to 31 December 2019. Seventy-nine subjects were assessed for eligibility, 6 were excluded and 73 were recruited for treatment.

The study included 2 phases, a safety run-in Phase 1 (Cohorts A1 and A2) and an expansion Phase 2, Cohorts B, C, C-FLOT and D/D2.

Pre-assignment

Screening details:

Screening was completed within 28 days of the start of therapy.

Subjects must have had a histological diagnosis of oesophageal or gastroesophageal cancer and have not received prior chemotherapy.

Cohorts A and B - metastatic/locally advanced cancer.

Cohorts C, C-FLOT and D/D2 - deemed suitable for surgery with curative intent.

Period 1

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

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort A1 |

Arm description:

Metastatic/locally Advanced Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | Imfinzi |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for up to 11 doses.

| | |
|--|-----------------------|
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | Eloxatin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Oxaliplatin (130 mg/m²) was administered by intravenous infusion in six three-week cycles starting on the day of the third dose of durvalumab.

| | |
|--|--------------|
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | Xeloda |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine (1250 mg/m²/day) was given orally in two divided doses for six three-week cycles starting on the day of the first oxaliplatin infusion.

| | |
|------------------|-----------|
| Arm title | Cohort A2 |
|------------------|-----------|

Arm description:

Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | Imfinzi |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for up to 11 doses.

| | |
|--|-----------------------|
| Investigational medicinal product name | Tremelimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

One dose of tremelimumab (37.5 mg) was given by intravenous infusion on the same day as the first dose of durvalumab.

| | |
|--|-----------------------|
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | Eloxatin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Oxaliplatin (130 mg/m²) was administered by intravenous infusion in six three-week cycles starting on the day of the third dose of durvalumab.

| | |
|--|--------------|
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | Xeloda |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine (1250 mg/m²/day) was given orally in two divided doses for six three-week cycles starting on the day of the first oxaliplatin infusion.

| | |
|------------------|----------|
| Arm title | Cohort B |
|------------------|----------|

Arm description:

Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | Imfinzi |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for up to 11 doses.

| | |
|--|--------------|
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | Xeloda |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

| | |
|---|-----------------------|
| Dosage and administration details: | |
| Capecitabine (1250 mg/m ² /day) was given orally in two divided doses for six three-week cycles starting on the day of the first oxaliplatin infusion. | |
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | Eloxatin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Oxaliplatin (130 mg/m ²) was administered by intravenous infusion in six three-week cycles starting on the day of the third dose of durvalumab. | |
| Investigational medicinal product name | Tremelimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| One dose of tremelimumab (75 mg) was given by intravenous infusion on the same day as the first dose of durvalumab. | |
| Arm title | Cohort C |
| Arm description: | |
| Operable Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Arm type | Experimental |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | Imfinzi |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Durvalumab (750 mg every two weeks [Q2W]) was given for 11 doses. | |
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | Eloxatin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Oxaliplatin (130 mg/m ²) was administered by intravenous infusion in six three-week cycles starting on the day of the third dose of durvalumab. | |
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | Xeloda |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Capecitabine (1250 mg/m ² /day) was given orally in two divided doses for six three-week cycles starting on the day of the first oxaliplatin infusion. | |
| Arm title | Cohort C-FLOT |
| Arm description: | |
| Operable Oesophageal Cancer, Durvalumab + Neoadjuvant 5-fluorouracil (5-FU), Leucovorin, Oxaliplatin, and Docetaxel (FLOT) Chemotherapy | |
| Arm type | Experimental |

| | |
|--|-----------------------|
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | Imfinzi |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for 6 doses prior to surgery. Optional durvalumab for up to a total of 12 doses was allowed after recovery from surgery provided this was within 3 months of surgery.

| | |
|--|-----------------------|
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | Eloxatin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

As part of two cycles of neoadjuvant FLOT chemotherapy, oxaliplatin (85 mg/m²) was administered by intravenous infusion before surgery starting on the day of the third dose of durvalumab. Subjects were to undergo surgery 6 to 8 weeks after completing chemotherapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions), FLOT or durvalumab plus FLOT at the discretion of the Investigator once recovered from surgery, provided that this was within 3 months of surgery.

| | |
|--|-----------------------|
| Investigational medicinal product name | 5-Flourouracil |
| Investigational medicinal product code | |
| Other name | 5-FU |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

As part of two cycles of neoadjuvant FLOT chemotherapy, 5-fluorouracil (5-FU) (2600 mg/m²) was administered as a 24-hr infusion before surgery starting on the day of the third dose of durvalumab. Subjects were to undergo surgery 6 to 8 weeks after completing chemotherapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions), FLOT or durvalumab plus FLOT at the discretion of the Investigator once recovered from surgery, provided that this was within 3 months of surgery.

| | |
|--|-----------------------|
| Investigational medicinal product name | Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

As part of two cycles of neoadjuvant FLOT chemotherapy, leucovorin (200 mg/m² IV), was administered before surgery starting on the day of the third dose of durvalumab. Subjects were to undergo surgery 6 to 8 weeks after completing chemotherapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions), FLOT or durvalumab plus FLOT at the discretion of the Investigator once recovered from surgery, provided that this was within 3 months of surgery.

| | |
|--|-----------------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | Taxotere |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

As part of two cycles of neoadjuvant FLOT chemotherapy, docetaxel (50 mg/m²) was administered before surgery starting on the day of the third dose of durvalumab. Subjects were to undergo surgery 6 to 8 weeks after completing chemotherapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions), FLOT or durvalumab plus FLOT at the discretion of the Investigator once recovered from surgery, provided that this was within 3

months of surgery.

| | |
|------------------|-------------|
| Arm title | Cohort D/D2 |
|------------------|-------------|

Arm description:

Operable Oesophageal Cancer, Durvalumab + Neoadjuvant Chemo(radio)therapy with Paclitaxel, Carboplatin and Radiotherapy.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | Imfinzi |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for 2 doses (Cohort D) or 5 doses (Cohort D2) prior to surgery. Optional durvalumab dosing was allowed after recovery from surgery for up to 12 total doses provided that this was within 3 months of surgery.

| | |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | Taxol |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Five weekly doses of paclitaxel (50 mg/m²) by intravenous infusion as part of neoadjuvant chemoradiotherapy (41.4 Gy radiotherapy given over 23 fractions) were administered before surgery. In Cohort D2, subjects continued durvalumab for 3 additional doses while receiving chemoradiation. Subjects were to undergo surgery 6 to 8 weeks after completing chemo(radio)therapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this was within 3 months of surgery.

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | Paraplatin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Five weekly doses of carboplatin (AUC 2) by intravenous infusion as part of neoadjuvant chemoradiotherapy (41.4 Gy radiotherapy given over 23 fractions) were administered before surgery. In Cohort D2, subjects continued durvalumab for 3 additional doses while receiving chemoradiation. Subjects were to undergo surgery 6 to 8 weeks after completing chemo(radio)therapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this was within 3 months of surgery.

| Number of subjects in period 1 | Cohort A1 | Cohort A2 | Cohort B |
|---------------------------------------|-----------|-----------|----------|
| Started | 12 | 5 | 21 |
| Completed | 8 | 2 | 13 |
| Not completed | 4 | 3 | 8 |
| Adverse event, serious fatal | 1 | 1 | - |
| Consent withdrawn by subject | - | 1 | - |

| | | | |
|--------------------------|---|---|---|
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | - | - | 4 |
| Progressive disease | 3 | 1 | 3 |

| Number of subjects in period 1 | Cohort C | Cohort C-FLOT | Cohort D/D2 |
|---------------------------------------|----------|---------------|-------------|
| Started | 11 | 9 | 15 |
| Completed | 11 | 9 | 13 |
| Not completed | 0 | 0 | 2 |
| Adverse event, serious fatal | - | - | - |
| Consent withdrawn by subject | - | - | - |
| Physician decision | - | - | - |
| Adverse event, non-fatal | - | - | - |
| Progressive disease | - | - | 2 |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Cohort A1 |
| Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Reporting group title | Cohort A2 |
| Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Reporting group title | Cohort B |
| Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Reporting group title | Cohort C |
| Reporting group description: Operable Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Reporting group title | Cohort C-FLOT |
| Reporting group description: Operable Oesophageal Cancer, Durvalumab + Neoadjuvant 5-fluorouracil (5-FU), Leucovorin, Oxaliplatin, and Docetaxel (FLOT) Chemotherapy | |
| Reporting group title | Cohort D/D2 |
| Reporting group description: Operable Oesophageal Cancer, Durvalumab + Neoadjuvant Chemo(radio)therapy with Paclitaxel, Carboplatin and Radiotherapy. | |

| Reporting group values | Cohort A1 | Cohort A2 | Cohort B |
|---------------------------------------|-----------|-----------|----------|
| Number of subjects | 12 | 5 | 21 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 7 | 3 | 16 |
| From 65-84 years | 5 | 2 | 5 |
| Age continuous Units: years | | | |
| median | 59.5 | 55.0 | 58.0 |
| full range (min-max) | 23 to 75 | 29 to 67 | 42 to 78 |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 1 | 4 |
| Male | 10 | 4 | 17 |

| Reporting group values | Cohort C | Cohort C-FLOT | Cohort D/D2 |
|------------------------------------|----------|---------------|-------------|
| Number of subjects | 11 | 9 | 15 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 8 | 6 | 7 |
| From 65-84 years | 3 | 3 | 8 |

| | | | |
|--|------------------|------------------|------------------|
| Age continuous Units: years median full range (min-max) | 57.0 46 to 71 | 56.0 33 to 72 | 65.0 50 to 72 |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 1 | 3 |
| Male | 11 | 8 | 12 |

| | | | |
|--|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 73 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 47 | | |
| From 65-84 years | 26 | | |
| Age continuous Units: years median full range (min-max) | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 11 | | |
| Male | 62 | | |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Cohort A1 |
| Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Reporting group title | Cohort A2 |
| Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Reporting group title | Cohort B |
| Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Reporting group title | Cohort C |
| Reporting group description: Operable Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy | |
| Reporting group title | Cohort C-FLOT |
| Reporting group description: Operable Oesophageal Cancer, Durvalumab + Neoadjuvant 5-fluorouracil (5-FU), Leucovorin, Oxaliplatin, and Docetaxel (FLOT) Chemotherapy | |
| Reporting group title | Cohort D/D2 |
| Reporting group description: Operable Oesophageal Cancer, Durvalumab + Neoadjuvant Chemo(radio)therapy with Paclitaxel, Carboplatin and Radiotherapy. | |

Primary: Number of Subjects With Best Overall Tumor Response by the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

| | |
|--|--|
| End point title | Number of Subjects With Best Overall Tumor Response by the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) ^[1] |
| End point description: Tumor responses were evaluated using appropriate imaging and categorized according to irRECIST at Screening (up to 28 days before the first dose of study treatment), and in Cycles 1, 3, 5 and 6 in Cohorts A1, A2 and B. In the other cohorts, tumor response was assessed at baseline, post-surgery and 14 days after the last dose. In Cohort C-FLOT, an additional assessment was done prior to surgery and in Cohorts C and D, an additional assessment was done in Cycle 3. Per irRECIST, measurable lesions are categorized as follows: Immune-related Complete Response (irCR): Complete disappearance of all target lesions; Immune-related Partial Response (irPR): $\geq 30\%$ decrease from baseline in the total measurable tumor burden (TMTB); Immune-related Progressive Disease (irPD): $\geq 20\%$ increase from nadir in TMTB; Immune-related Stable Disease (irSD): not meeting above criteria; irNon-CR/Non-PD: not evaluable. | |
| End point type | Primary |
| End point timeframe: up to 1 year | |
| 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: In this study where different regimens are being studied in each Cohort, the primary objective was to assess the safety of the different regimens and sample sizes were determined based on this. While secondary objectives were to obtain preliminary efficacy of each regimen, the intent was not to compare the regimens and as a results no statistical comparisons were made between cohorts. | |

| End point values | Cohort A1 | Cohort A2 | Cohort B | Cohort C |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 5 | 20 | 9 |
| Units: subjects | | | | |
| irCR | 2 | 0 | 0 | 3 |
| irPR | 3 | 3 | 10 | 1 |
| irSD | 5 | 1 | 4 | 0 |
| irPD | 1 | 1 | 5 | 1 |
| irNon-CR/Non-PD | 0 | 0 | 1 | 1 |
| Not Evaluable | 0 | 0 | 0 | 3 |

| End point values | Cohort C-FLOT | Cohort D/D2 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 8 | | |
| Units: subjects | | | | |
| irCR | 1 | 2 | | |
| irPR | 0 | 0 | | |
| irSD | 0 | 0 | | |
| irPD | 0 | 1 | | |
| irNon-CR/Non-PD | 0 | 0 | | |
| Not Evaluable | 4 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Metastatic/locally Advanced Oesophageal Cancer (OC) Who Had a Response at Cycle 6 by irRECIST

| | |
|-----------------|--|
| End point title | Number of Subjects With Metastatic/locally Advanced Oesophageal Cancer (OC) Who Had a Response at Cycle 6 by irRECIST ^[2] |
|-----------------|--|

End point description:

Tumor responses were evaluated using appropriate imaging and categorized according to irRECIST at Screening (up to 28 days before the first dose of study treatment), and in Cycles 1, 3, 5 and 6 in Cohorts A1, A2 and B. Per irRECIST, measurable lesions are categorized as follows: irCR: Complete disappearance of all target lesions; irPR: $\geq 30\%$ decrease from baseline in the total measurable tumor burden (TMTB); irPD: $\geq 20\%$ increase from nadir in TMTB; irSD: not meeting above criteria; irNon-CR/Non-PD: not evaluable.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 23 weeks.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: In this study where different regimens are being studied in each Cohort, the primary objective was to assess the safety of the different regimens and sample sizes were determined based on this. While secondary objectives were to obtain preliminary efficacy of each regimen, the intent was not to compare the regimens and as a results no statistical comparisons were made between cohorts.

| End point values | Cohort A1 | Cohort A2 | Cohort B | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 3 | 14 | |
| Units: Number of subjects | | | | |
| irCR | 2 | 0 | 0 | |
| irPR | 2 | 2 | 7 | |
| irSD | 3 | 1 | 4 | |
| irPD | 1 | 0 | 1 | |
| irNonCR/Non-PD | 0 | 0 | 1 | |
| Not evaluable | 0 | 0 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression-free Survival (PFS) by irRECIST as Estimated Using the Kaplan-Meier Method

| | |
|---|---|
| End point title | Median Progression-free Survival (PFS) by irRECIST as Estimated Using the Kaplan-Meier Method |
| End point description: | |
| <p>In Cohorts A1, A2 and B, PFS was measured from the date of the first dose of study treatment to the date of earliest disease progression according to irRECIST or to the date of death, if disease progression did not occur.</p> <p>For subjects in Cohorts C/C-FLOT and D/D2 undergoing successful surgery, post-operative PFS was measured with time origin at the day of surgery until the first occurrence of confirmed progression by irRECIST or date of death if the subject dies from any causes before progression.</p> <p>Per irRECIST, irPD was defined as a $\geq 20\%$ increase from nadir in the TMTB.</p> <p>The median was not reached in Cohort C-FLOT, this is indicated by 999. The upper 95% confidence interval limit was not reached in Cohorts A2, C, C-FLOT and D, this has been indicated by 999.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 1 year | |

| End point values | Cohort A1 | Cohort A2 | Cohort B | Cohort C |
|----------------------------------|-------------------|------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 5 | 21 | 11 |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.7 (0.9 to 29.1) | 5.2 (1.4 to 999) | 11.9 (3.9 to 15.6) | 25.40 (6.47 to 999) |

| End point values | Cohort C-FLOT | Cohort D/D2 | | |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 14 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 32.03 (2.10 to 999) | 999 (9.59 to 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival (OS) as Estimated Using the Kaplan-Meier Method

| | |
|-----------------|---|
| End point title | Median Overall Survival (OS) as Estimated Using the Kaplan-Meier Method |
|-----------------|---|

End point description:

After completion of treatment, all subjects were followed for survival every 6 months for up to 3 years from start of treatment. OS was measured from the date of the first dose of study treatment to the date of death or last follow-up. Subjects lost to follow-up were censored on the date when they were last known to be alive. Per protocol amendment 8.0, all post study follow-up for the collection of survival data was discontinued as of 30 June 2022.

The medians were not estimable for Cohorts C, C-FLOT and D/D2, this has been indicated by a median which is indicated as 999. The upper 95% confidence interval limit was not reached in Cohorts A, A2, C, C-FLOT and D/D2, this has been indicated by 999.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 30 June 2022

| End point values | Cohort A1 | Cohort A2 | Cohort B | Cohort C |
|----------------------------------|-------------------|------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 5 | 21 | 11 |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.8 (3.1 to 999) | 8.6 (2.7 to 999) | 15.6 (9.3 to 33.5) | 999 (18.46 to 999) |

| End point values | Cohort C-FLOT | Cohort D/D2 | | |
|----------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 15 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (8.02 to 999) | 999 (13.14 to 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: One Year Survival Rate in Subjects with Operable OC

| | |
|-----------------|--|
| End point title | One Year Survival Rate in Subjects with Operable OC ^[3] |
|-----------------|--|

End point description:

After completion of treatment, all subjects were followed for survival every 6 months for up to 3 years from start of treatment. OS was measured from the date of the first dose of study treatment to the date of death or last follow-up. Subjects lost to follow-up were censored on the date when they were last known to be alive. Per protocol amendment 8.0, all post study follow-up for the collection of survival data was discontinued as of 30 June 2022.

In Cohort C, both the upper and lower limits of the 95% confidence interval were not reached, this has been indicated by 0 and 999 respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 1 year

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: In this study where different regimens are being studied in each Cohort, the primary objective was to assess the safety of the different regimens and sample sizes were determined based on this. While secondary objectives were to obtain preliminary efficacy of each regimen, the intent was not to compare the regimens and as a results no statistical comparisons were made between cohorts.

| End point values | Cohort C | Cohort C-FLOT | Cohort D/D2 | |
|----------------------------------|-----------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 9 | 15 | |
| Units: Percent | | | | |
| number (confidence interval 95%) | 100 (0 to 999) | 89.0 (43.3 to 98.4) | 86.7 (56.4 to 96.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Prior to Surgery in Operable OC (Cohorts C, C-FLOT and D/D2) using Positron Emission Tomography (PET) Response Criteria in Solid Tumors (PERCIST)

| | |
|-----------------|---|
| End point title | Overall Response Prior to Surgery in Operable OC (Cohorts C, C-FLOT and D/D2) using Positron Emission Tomography (PET) Response Criteria in Solid Tumors (PERCIST) ^[4] |
|-----------------|---|

End point description:

18 fluorodeoxyglucose (18F-FDG) PET scans were conducted at baseline and in Cycle 3 in Cohorts C and D, and after completion of therapy in Cohort C-FLOT and D2. Complete metabolic response: 18F-FDG-avid lesions revert to background of normal tissues in which they are located; Partial metabolic response: 30% or greater reduction in measurable tumors; Stable Metabolic Response: no visible change in metabolic activity of tumor; Progressive metabolic disease: increase in intensity or extent of tumor metabolic activity or new sites of activity.

All operable OC patients in Cohorts C, C-FLOT and D/D2 who had a baseline PET scan and a PET scan prior to surgery were included in the analyses.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

After completion of therapy and prior to surgery.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: In this study where different regimens are being studied in each Cohort, the primary objective was to assess the safety of the different regimens and sample sizes were determined based on this. While secondary objectives were to obtain preliminary efficacy of each regimen, the intent was not

to compare the regimens and as a results no statistical comparisons were made between cohorts.

| End point values | Cohort C | Cohort C-FLOT | Cohort D/D2 | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 6 | 13 | |
| Units: Subjects | | | | |
| Complete Metabolic Response | 2 | 1 | 3 | |
| Partial Metabolic Response | 5 | 3 | 7 | |
| Stable Disease | 1 | 2 | 1 | |
| Progressive Disease | 3 | 0 | 2 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring between the signing of informed consent and the off-study date (i.e., through 110 days after the last dose of study treatment) were documented, regardless of a causal relationship to study drug.

Adverse event reporting additional description:

AE documentation included onset/resolution dates, severity using NCI CTCAE (version 4.03), seriousness, relationship to study drug, study drug action taken, treatment and outcome. Preferred terms were counted once per subject at the maximum reported grade.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Cohort A1 |
|-----------------------|-----------|

Reporting group description:

Metastatic/locally advanced Oesophageal Cancer, Durvalumab + Oxaliplatin/Capcitabine Chemotherapy

| | |
|-----------------------|-----------|
| Reporting group title | Cohort A2 |
|-----------------------|-----------|

Reporting group description:

Metastatic/locally advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capcitabine Chemotherapy

| | |
|-----------------------|----------|
| Reporting group title | Cohort B |
|-----------------------|----------|

Reporting group description:

Metastatic/locally advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capcitabine Chemotherapy

| | |
|-----------------------|----------|
| Reporting group title | Cohort C |
|-----------------------|----------|

Reporting group description:

Operable Oesophageal Cancer; Durvalumab + Oxaliplatin/Capcitabine Chemotherapy

| | |
|-----------------------|---------------|
| Reporting group title | Cohort C-FLOT |
|-----------------------|---------------|

Reporting group description:

Operable Oesophageal Cancer, Durvalumab + FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) Chemotherapy

| | |
|-----------------------|-------------|
| Reporting group title | Cohort D/D2 |
|-----------------------|-------------|

Reporting group description:

Operable Oesophageal Cancer, Durvalumab + Neoadjuvant Chemo(radio)therapy with Paclitaxel, Carboplatin and radiotherapy.

| Serious adverse events | Cohort A1 | Cohort A2 | Cohort B |
|---|-----------------|----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 12 (58.33%) | 4 / 5 (80.00%) | 12 / 21 (57.14%) |
| number of deaths (all causes) | 9 | 5 | 16 |
| number of deaths resulting from adverse events | 3 | 2 | 4 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 5 (20.00%) | 4 / 21 (19.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 4 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Jejunostomy refashioning | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagectomy | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Encephalitis autoimmune | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (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 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 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 |
| Colitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Enteritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (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 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (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 / 12 (0.00%) | 2 / 5 (40.00%) | 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 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|----------------|
| Urinary retention | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (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 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|----------------|----------------|
| Lower respiratory tract infection subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orchitis subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Postoperative wound infection subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 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 |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|---------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort C | Cohort C-FLOT | Cohort D/D2 |
|--|-----------------|----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 11 (63.64%) | 6 / 9 (66.67%) | 10 / 15 (66.67%) |
| number of deaths (all causes) | 5 | 2 | 6 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Jejunostomy refashioning | | | |

| | | | |
|--|----------------|---------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagectomy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 15 (13.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (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 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Encephalitis autoimmune | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (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 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 3 / 15 (20.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|----------------|----------------|----------------|
| disorders | | | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| 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 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (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 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|-----------------|
| Orchitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 15 (13.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (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 |

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

| Non-serious adverse events | Cohort A1 | Cohort A2 | Cohort B |
|---|-------------------|-----------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | 5 / 5 (100.00%) | 21 / 21 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Flushing | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Orthostatic hypotension | | | |

| | | | |
|--|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 | 1 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 3 | 1 | 1 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 0 | 0 | 3 |
| Chills | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Early satiety | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 10 / 12 (83.33%) | 5 / 5 (100.00%) | 13 / 21 (61.90%) |
| occurrences (all) | 16 | 10 | 23 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 2 | 2 |
| Infusion site reaction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal inflammation | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 3 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 5 (40.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Temperature intolerance | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 2 / 5 (40.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 4 | 2 | 5 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 5 (40.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 2 | 3 | 6 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laryngospasm | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 5 (40.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Nasal congestion | | | |

| | | | |
|------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 2 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 1 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 5 (40.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Depression | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 3 | 1 | 1 |
| Irritability | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 0 | 0 | 8 |
| Amylase increased | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 5 (20.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 5 | 1 | 10 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 5 / 21 (23.81%) |
| occurrences (all) | 0 | 0 | 8 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 1 | 0 | 5 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood iron decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 10 | 0 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 2 |
| Platelet count decreased | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 2 | 0 | 4 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 5 | 0 | 4 |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 5 (60.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 5 | 3 | 6 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 2 | 0 | 1 |
| Dumping syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Wound complication | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wound haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |

| | | | |
|---------------------------------|-----------------|----------------|-----------------|
| Palpitations | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysaesthesia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 1 | 0 | 3 |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Head discomfort | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 5 (20.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 2 | 1 | 2 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle contractions involuntary | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 2 / 5 (40.00%) | 6 / 21 (28.57%) |
| occurrences (all) | 6 | 2 | 10 |
| Paraesthesia | | | |

| | | | |
|--------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 5 (20.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 6 | 1 | 3 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 1 / 5 (20.00%) | 5 / 21 (23.81%) |
| occurrences (all) | 9 | 1 | 5 |
| Poor quality sleep | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 1 / 5 (20.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 10 | 6 | 12 |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 5 (20.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 9 | 1 | 9 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 1 / 5 (20.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 12 | 2 | 8 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| Blepharospasm subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Dry eye subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Eye pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Vision blurred subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 0 / 5 (0.00%) 0 | 2 / 21 (9.52%) 3 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 2 / 5 (40.00%) 2 | 2 / 21 (9.52%) 2 |
| Abdominal distension subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 4 / 12 (33.33%) 5 | 1 / 5 (20.00%) 1 | 3 / 21 (14.29%) 3 |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Colitis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 5 / 12 (41.67%) 7 | 4 / 5 (80.00%) 5 | 5 / 21 (23.81%) 7 |
| Diarrhoea | | | |

| | | | |
|----------------------------------|-----------------|----------------|------------------|
| subjects affected / exposed | 7 / 12 (58.33%) | 2 / 5 (40.00%) | 11 / 21 (52.38%) |
| occurrences (all) | 14 | 3 | 22 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 3 / 5 (60.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 6 | 5 | 5 |
| Epigastric discomfort | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Eructation | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Melaena | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |

| | | | |
|-----------------------------|------------------|----------------|------------------|
| subjects affected / exposed | 10 / 12 (83.33%) | 4 / 5 (80.00%) | 12 / 21 (57.14%) |
| occurrences (all) | 17 | 7 | 24 |
| Lip pruritus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malabsorption | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oesophageal fistula | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Retching | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Sensitivity of teeth | | | |

| | | | |
|--|------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Steatorrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 | 1 |
| Tongue coated | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 11 / 12 (91.67%) | 2 / 5 (40.00%) | 8 / 21 (38.10%) |
| occurrences (all) | 15 | 11 | 14 |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Dermatitis psoriasiform | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 5 | 1 | 1 |
| Erythema | | | |

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|--|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 5 / 21 (23.81%) |
| occurrences (all) | 2 | 0 | 8 |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 5 / 21 (23.81%) |
| occurrences (all) | 0 | 0 | 7 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Rash | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 0 | 1 | 3 |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------------|---------------------|---------------------|
| Swelling face subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Systemic lupus erythematosus rash subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Endocrine disorders | | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 21 (0.00%) 0 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 1 / 5 (20.00%) 1 | 0 / 21 (0.00%) 0 |
| Adrenal insufficiency subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 | 2 / 21 (9.52%) 2 |
| Arthritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 4 | 0 / 5 (0.00%) 0 | 2 / 21 (9.52%) 2 |
| Flank pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Jaw disorder subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Limb discomfort subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Muscle spasms | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 2 | 1 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 1 | 3 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myopathy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Infections and infestations | | | |
| Balanitis candida | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|-----------------------------------|-----------------|---------------|-----------------|
| Cystitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 0 | 0 | 4 |
| Medical device site infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 3 | 0 | 1 |
| Oropharyngeal candidiasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|------------------------------------|-----------------|----------------|-----------------|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 5 (40.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 2 | 2 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 0 | 0 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 5 (60.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 2 | 6 | 4 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 5 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gout | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 2 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 5 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 4 | 1 | 1 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 5 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |

| Non-serious adverse events | Cohort C | Cohort C-FLOT | Cohort D/D2 |
|---|-------------------|-----------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 11 (100.00%) | 9 / 9 (100.00%) | 15 / 15 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 15 (6.67%) 2 |
| Skin papilloma subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Tumour pain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Vascular disorders | | | |
| Deep vein thrombosis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Flushing subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Orthostatic hypotension subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Phlebitis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Chest discomfort subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Chest pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 2 / 15 (13.33%) 2 |
| Chills | | | |

| | | | |
|---------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Early satiety | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 7 / 11 (63.64%) | 6 / 9 (66.67%) | 8 / 15 (53.33%) |
| occurrences (all) | 17 | 11 | 18 |
| Feeling cold | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infusion site reaction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Temperature intolerance | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 11 (54.55%) | 2 / 9 (22.22%) | 5 / 15 (33.33%) |
| occurrences (all) | 6 | 2 | 6 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 1 / 9 (11.11%) | 3 / 15 (20.00%) |
| occurrences (all) | 3 | 1 | 3 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 2 / 15 (13.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Laryngospasm | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Confusional state | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 15 (13.33%) |
| occurrences (all) | 0 | 0 | 3 |
| Irritability | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 2 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Blood iron decreased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood thyroid stimulating hormone decreased | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Blood urea increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 9 (22.22%) 2 | 0 / 15 (0.00%) 0 |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 15 (0.00%) 0 |
| Lipase increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 2 | 0 / 15 (0.00%) 0 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Transaminases increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 3 | 0 / 9 (0.00%) 0 | 4 / 15 (26.67%) 8 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Dumping syndrome subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 3 / 15 (20.00%) 4 |
| Fall | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound complication | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 2 / 15 (13.33%) |
| occurrences (all) | 0 | 1 | 2 |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 3 | 1 | 1 |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 3 / 9 (33.33%) | 1 / 15 (6.67%) |
| occurrences (all) | 4 | 3 | 1 |
| Head discomfort | | | |

| | | | |
|--------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 2 / 15 (13.33%) |
| occurrences (all) | 1 | 1 | 2 |
| Lethargy | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Muscle contractions involuntary | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 6 / 11 (54.55%) | 4 / 9 (44.44%) | 0 / 15 (0.00%) |
| occurrences (all) | 11 | 6 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Poor quality sleep | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 2 | 0 | 1 |
| Tremor | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| Anaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 3 / 9 (33.33%) 3 | 5 / 15 (33.33%) 6 |
| Neutropenia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 9 (22.22%) 3 | 3 / 15 (20.00%) 3 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 15 (13.33%) 2 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Eye disorders Blepharospasm subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Dry eye subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Eye pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Abdominal distension subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 9 (11.11%) 2 | 2 / 15 (13.33%) 3 |
| Abdominal pain lower | | | |

| | | | |
|----------------------------------|-----------------|----------------|------------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 2 / 15 (13.33%) |
| occurrences (all) | 2 | 2 | 2 |
| Colitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 4 / 9 (44.44%) | 5 / 15 (33.33%) |
| occurrences (all) | 1 | 5 | 5 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | 7 / 9 (77.78%) | 10 / 15 (66.67%) |
| occurrences (all) | 13 | 11 | 27 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 4 / 15 (26.67%) |
| occurrences (all) | 0 | 4 | 5 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 3 | 1 | 1 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 3 / 9 (33.33%) | 3 / 15 (20.00%) |
| occurrences (all) | 2 | 4 | 4 |
| Epigastric discomfort | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Eructation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 3 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | 3 / 9 (33.33%) | 3 / 15 (20.00%) |
| occurrences (all) | 5 | 4 | 4 |
| Haemorrhoidal haemorrhage | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | 5 / 9 (55.56%) | 9 / 15 (60.00%) |
| occurrences (all) | 6 | 6 | 17 |
| Lip pruritus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Malabsorption | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Oesophageal fistula | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 5 / 15 (33.33%) |
| occurrences (all) | 0 | 2 | 6 |
| Oral pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pancreatitis | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Retching | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sensitivity of teeth | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Steatorrhoea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tongue coated | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 3 / 9 (33.33%) | 6 / 15 (40.00%) |
| occurrences (all) | 1 | 3 | 8 |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis psoriasiform | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Night sweats | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 2 / 15 (13.33%) |
| occurrences (all) | 2 | 1 | 4 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 4 / 9 (44.44%) | 5 / 15 (33.33%) |
| occurrences (all) | 0 | 4 | 6 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Rash generalised subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Rash macular subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 15 (0.00%) 0 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Rash pruritic subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Systemic lupus erythematosus rash subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Endocrine disorders | | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 9 (11.11%) 1 | 1 / 15 (6.67%) 1 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 9 (11.11%) 2 | 1 / 15 (6.67%) 2 |
| Adrenal insufficiency subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 9 (11.11%) 1 | 1 / 15 (6.67%) 1 |
| Arthritis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Back pain | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Jaw disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Limb discomfort | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 2 / 15 (13.33%) |
| occurrences (all) | 0 | 3 | 2 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myopathy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Infections and infestations | | | |
| Balanitis candida | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Medical device site infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 2 | 1 |
| Nail infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------------|-----------------|----------------|-----------------|
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 9 (22.22%) | 2 / 15 (13.33%) |
| occurrences (all) | 1 | 2 | 2 |
| Oropharyngeal candidiasis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 15 (13.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 2 | 1 | 1 |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|------------------------------------|-----------------|----------------|-----------------|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 5 / 9 (55.56%) | 5 / 15 (33.33%) |
| occurrences (all) | 2 | 6 | 12 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gout | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 3 / 15 (20.00%) |
| occurrences (all) | 0 | 2 | 3 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 1 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypophosphataemia | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 9 (22.22%) | 2 / 15 (13.33%) |
| occurrences (all) | 1 | 2 | 2 |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 14 July 2017 | Change to treatment regimen in Cohort D (neoadjuvant chemoradiotherapy before surgery in operable oesophageal cancer): The oxaliplatin-capecitabine backbone of the CRT regimen was replaced with a paclitaxel/carboplatin regimen. |
| 08 September 2017 | <p>Additional requirements for carboplatin and paclitaxel treatment.</p> <p>Women of childbearing potential should avoid becoming pregnant while taking carboplatin and paclitaxel; they should notify the treating physician immediately if pregnancy occurs. Female and male subjects of fertile age and/or their partners should use contraceptives during and for at least 6 months after treatment with these drugs.</p> <p>Male subjects should also avoid sperm donation during and for at least 6 months after treatment with these drugs.</p> <p>Breastfeeding should be discontinued for the duration of treatment with these drugs.</p> <p>Male subjects should be advised regarding cryoconservation of sperm prior to treatment because of the possibility of irreversible infertility due to the treatment.</p> <p>CYP2C8 or CYP3A4 inhibitors/inducers: Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.</p> <p>Nephrotoxic/ototoxic drugs: Auditory defects have been reported during carboplatin therapy. Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics is not recommended as they may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.</p> |
| 10 March 2018 | <p>The eligibility criteria have been amended to exclude patients who have received prior full dose chemotherapy, this enables collection of a pre-treatment biopsy for the planned biomarker analysis (tertiary endpoint). This eligibility criteria was originally included in the protocol and was removed from the protocol in error during a previous protocol amendment.</p> <p>Elevations of amylase and lipase are expected adverse events for durvalumab or the combination of durvalumab and tremelimumab and the study requires regular testing of both as potential indicators of pancreatitis. The dose limiting toxicity definitions have been clarified to exclude grade 3+ asymptomatic increases in amylase or lipase, which show no clinical evidence of pancreatitis. Grade 3+ pancreatitis remains a dose limiting toxicity.</p> <p>Expected adverse events have been added to the protocol, based on the durvalumab and tremelimumab dose modifications guidelines (updated Nov 2017). The events added are myocarditis (previously listed under 'other inflammatory responses'), myositis/polymyositis and some new events added to 'other inflammatory responses'.</p> <p>Clarification has been added to indicate that surgery timing is according to institutional policies. The study was initially set-up as a single site study and the 6-8 weeks post treatment timeframe for surgery was as per standard of care at that site alone. Surgery may be delayed at any site as per clinical need.</p> |

| | |
|-----------------|--|
| 20 July 2018 | <p>The chemotherapy backbone administered in Cohort C was updated due to changes in standard of care treatment in the UK. The new cohort was referred to as Cohort C-FLOT which is a regimen combining 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel.</p> <p>Based on emerging data, a proposal was made to add Cohort C-FLOT to the study, in addition to Cohort C. The proposal for Cohort C-FLOT includes the following:</p> <ol style="list-style-type: none"> 1. Replace Oxaliplatin and capecitabine as neoadjuvant chemotherapy with the FLOT regimen to run concurrently with durvalumab treatment. 2. Introduce post-operative chemotherapy, also with FLOT. This will run concurrently with durvalumab immunotherapy. 3. Subjects allocated to oxaliplatin and capecitabine in Cohort C before the introduction of Cohort C-FLOT will not be replaced and will be included in the total 20 Subjects for Cohort C + Cohort C-FLOT. <p>The protocol will now include the collection of saliva samples for translational research at the same time point as the research biopsy (3 timepoints, baseline, immunotherapy only D22 and at end of treatment/day of surgery).</p> <p>Patients will be asked to consent to use of photographs of their alimentary tract taken during the biopsy procedure.</p> <p>Videos are taken as standard of care of the biopsy for quality improvement and still pictures may also be taken as part of this procedure. These pictures will not be identifiable. Current patients may also be reconsented. This is an optional consent.</p> |
| 26 April 2019 | <p>The Investigator(s) had the option to approach subjects with long-term survival (PFS > 1 year, still in remission) from the metastatic cohorts (A and B) of the trial to request blood (up to 300 mL) for additional testing.</p> <p>Introduction of Cohort D2</p> <p>Cohort D2 is a subset of Cohort D subjects for whom durvalumab doses will continue during chemoradiotherapy, after the initial 4-week immunotherapy period. Enrollment was to proceed to Cohort D2, unless there was a medical reason to enroll a specific subject to Cohort D.</p> |
| 11 January 2022 | <p>The Post Study Follow-up for the collection of survival data was discontinued as of 30 June 2022. As of 30 June 2022, all subjects had completed treatment and On Study Follow-up and all but up to 8 subjects had completed the 3-year Post Study Follow-up, which would have occurred by December 2022 for the remaining subjects.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported