



## Clinical trial results:

### A Phase 1/2, Open-label, Multicenter Study to Investigate the Safety and Preliminary Efficacy of Combined Bempegaldesleukin (NKTR-214) and Pembrolizumab with or without Chemotherapy in Patients with Locally Advanced or Metastatic Solid Tumors

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-003474-35 |
| Trial protocol           | DE ES IT       |
| Global end of trial date | 05 July 2022   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 29 December 2022 |
| First version publication date | 29 December 2022 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | 16-214-05 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03138889 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Nektar Therapeutics   |
| Sponsor organisation address | 455 Mission Bay Boulevard South, San Francisco, United States,  |
| Public contact               | Clinical Trial Information Desk, Nektar Therapeutics, +1 855 482 8676, <a href="mailto:studyinquiry@nektar.com">studyinquiry@nektar.com</a> |
| Scientific contact           | Clinical Trial Information Desk, Nektar Therapeutics, +1 855 482 8676, <a href="mailto:studyinquiry@nektar.com">studyinquiry@nektar.com</a> |

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                       | 27 July 2022 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 05 July 2022 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

- To determine the ORR per blinded independent central review (BICR) by RECIST 1.1 of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated metastatic NSCLC.

Protection of trial subjects:

A risk-based approach to management, monitoring, and oversight of the study was implemented, including:

- Proactive risk management, addressing areas of project risk in a prospective manner to allow for planning and prevention of negative risk, while taking advantage of pre-identified positive opportunities for improvement of project objectives. This included risk planning, risk identification, qualitative analysis of the risks, quantitative analysis of the risks, risk response, and risk monitoring and control, with risks tracked in the study Risk Register
- A risk-based approach to site monitoring, utilizing a combination of onsite and remote monitoring visits:
  - o A volume-based monitoring strategy was employed with volume-based ("milestone event") triggering of onsite monitoring visits at clinical sites. Examples of volume-based milestone events were: number of patients enrolled, number of data points entered into electronic data capture (EDC) and number of case report forms (CRFs) ready for Source Data Verification (SDV) at a clinical site. Remote monitoring visits were triggered at high-enrolling sites, those with significant issues, or data backlog related to queries and missing pages only, as well as at sites with less than 80% SDV, or as otherwise approved by Nektar.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 09 June 2017 |
| 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 States: 96 |
| Country: Number of subjects enrolled | Spain: 44         |
| Country: Number of subjects enrolled | France: 1         |
| Country: Number of subjects enrolled | Germany: 20       |
| Country: Number of subjects enrolled | Italy: 1          |
| Worldwide total number of subjects   | 162               |
| EEA total number of subjects         | 66                |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 74 |
| From 65 to 84 years                       | 87 |
| 85 years and over                         | 1  |

## Subject disposition

### Recruitment

Recruitment details:

Please refer to "Subjects enrolled per country" section above.

### Pre-assignment

Screening details:

Patients with select locally advanced or metastatic solid tumors and measurable disease per RECIST 1.1: first- and second-line melanoma, NSCLC, urothelial carcinoma, HNSCC, and HCC for the dose optimization; first-line NSCLC for the dose expansion; and second-line NSCLC and first- and second-line urothelial carcinoma for before protocol amendment 5

### 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                                      |
| <b>Arm title</b>             | Cohort 0 (Before Protocol Amendment 5.0) |

Arm description:

Patients enrolled before Protocol Amendment 5.0

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | NKTR-214              |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Intravenous 0.006 mg/kg once every 3 weeks

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

Dosage and administration details:

100 mg

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

Dosage and administration details:

1200 mg

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Cohort 1a (dose optimization) |
|------------------|-------------------------------|

Arm description:

Patients enrolled in the 3 + 3 dose optimization schema (Cohort 1a) were to start NKTR-214 at a dose of 0.008 mg/kg once every 3 weeks (q3w) with pembrolizumab.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|   |                           |
|---|---------------------------|
| Investigational medicinal product name  | NKTR-214                  |
| Investigational medicinal product code  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:  |                           |
| Intravenous NKTR-214 0.008, 0.010, and 0.012 mg/kg once every 3 weeks                                 |                           |
| Investigational medicinal product name  | Pembrolizumab             |
| Investigational medicinal product code  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:  |                           |
| 100 mg  |                           |
| <b>Arm title</b>  | Cohort 2 (dose expansion) |
| Arm description:  |                           |
| Patients were to receive a dose of 0.006 mg/kg of NKTR-214 combined with pembrolizumab.               |                           |
| Arm type  | Experimental              |
| Investigational medicinal product name  | NKTR-214                  |
| Investigational medicinal product code  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:  |                           |
| Intravenous NKTR-214 0.006 mg/kg once every 3 weeks   |                           |
| Investigational medicinal product name  | Pembrolizumab             |
| Investigational medicinal product code  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:  |                           |
| 100 mg  |                           |
| <b>Arm title</b>  | Cohort 3 (dose expansion) |
| Arm description:  |                           |
| Patients were to receive a starting at a dose of 0.010 mg/kg of NKTR-214 combined with pembrolizumab. |                           |
| Arm type  | Experimental              |
| Investigational medicinal product name  | NKTR-214                  |
| Investigational medicinal product code  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:  |                           |
| Intravenous NKTR-214 0.010 mg/kg once every 3 weeks   |                           |
| Investigational medicinal product name  | Pembrolizumab             |
| Investigational medicinal product code  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:  |                           |
| 100 mg  |                           |

|   |                             |
|---|-----------------------------|
| <b>Arm title</b>  | Cohort 4/5 (dose expansion) |
| Arm description:  |                             |
| Following review of safety and efficacy data from Cohorts 2 and 3, a decision was to be made to initiate Cohorts 4 and 5. In Cohorts 4 and 5, patients were to receive 0.006 mg/kg of NKTR-214 combined with pembrolizumab and platinum-based chemotherapy. |                             |
| Arm type  | Experimental                |
| Investigational medicinal product name  | NKTR-214                    |
| Investigational medicinal product code  |                             |
| Other name  |                             |
| Pharmaceutical forms  | Solution for infusion       |
| Routes of administration  | Intravenous use             |
| Dosage and administration details:  |                             |
| Intravenous NKTR-214 0.006 mg/kg once every 3 weeks   |                             |
| Investigational medicinal product name  | Pembrolizumab               |
| Investigational medicinal product code  |                             |
| Other name  |                             |
| Pharmaceutical forms  | Solution for infusion       |
| Routes of administration  | Intravenous use             |
| Dosage and administration details:  |                             |
| 100 mg  |                             |

| <b>Number of subjects in period 1</b> | Cohort 0 (Before Protocol Amendment 5.0) | Cohort 1a (dose optimization) | Cohort 2 (dose expansion) |
|---------------------------------------|--|-------------------------------|---------------------------|
| Started                               | 35                                       | 18                            | 75                        |
| Completed                             | 0  | 0                             | 0                         |
| Not completed                         | 35                                       | 18                            | 75                        |
| Consent withdrawn by subject          | 10                                       | 3                             | 3                         |
| Death                                 | 22                                       | 9                             | 39                        |
| Sponsor decision                      | 3  | 6                             | 33                        |

| <b>Number of subjects in period 1</b> | Cohort 3 (dose expansion) | Cohort 4/5 (dose expansion) |
|---------------------------------------|---------------------------|-----------------------------|
| Started                               | 17                        | 17                          |
| Completed                             | 0                         | 0                           |
| Not completed                         | 17                        | 17                          |
| Consent withdrawn by subject          | -                         | 1                           |
| Death                                 | 5                         | 2                           |
| Sponsor decision                      | 12                        | 14                          |

## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | Cohort 0 (Before Protocol Amendment 5.0) |
| Reporting group description:  |  |
| Patients enrolled before Protocol Amendment 5.0   |  |
| Reporting group title   | Cohort 1a (dose optimization)            |
| Reporting group description:  |  |
| Patients enrolled in the 3 + 3 dose optimization schema (Cohort 1a) were to start NKTR-214 at a dose of 0.008 mg/kg once every 3 weeks (q3w) with pembrolizumab.  |  |
| Reporting group title   | Cohort 2 (dose expansion)                |
| Reporting group description:  |  |
| Patients were to receive a dose of 0.006 mg/kg of NKTR-214 combined with pembrolizumab.   |  |
| Reporting group title   | Cohort 3 (dose expansion)                |
| Reporting group description:  |  |
| Patients were to receive a starting at a dose of 0.010 mg/kg of NKTR-214 combined with pembrolizumab.   |  |
| Reporting group title   | Cohort 4/5 (dose expansion)              |
| Reporting group description:  |  |
| Following review of safety and efficacy data from Cohorts 2 and 3, a decision was to be made to initiate Cohorts 4 and 5. In Cohorts 4 and 5, patients were to receive 0.006 mg/kg of NKTR-214 combined with pembrolizumab and platinum-based chemotherapy. |  |

| Reporting group values            | Cohort 0 (Before Protocol Amendment 5.0) | Cohort 1a (dose optimization) | Cohort 2 (dose expansion) |
|-----------------------------------|--|-------------------------------|---------------------------|
| Number of subjects                | 35                                       | 18                            | 75                        |
| Age categorical                   |  |                               |                           |
| Units: Subjects                   |  |                               |                           |
| Adults (18-64 years)              | 16                                       | 8                             | 35                        |
| From 65-84 years                  | 18                                       | 10                            | 40                        |
| 85 years and over                 | 1  | 0                             | 0                         |
| Age continuous                    |  |                               |                           |
| Units: years                      |  |                               |                           |
| arithmetic mean                   | 67.2                                     | 62.6                          | 65.8                      |
| standard deviation                | ± 11.20                                  | ± 10.15                       | ± 9.30                    |
| Gender categorical                |  |                               |                           |
| Units: Subjects                   |  |                               |                           |
| Female                            | 11                                       | 11                            | 24                        |
| Male                              | 24                                       | 7                             | 51                        |
| Ethnicity                         |  |                               |                           |
| Units: Subjects                   |  |                               |                           |
| Hispanic or Latino                | 2  | 0                             | 3                         |
| Not Hispanic or Latino            | 30                                       | 18                            | 65                        |
| Not Reported                      | 0  | 0                             | 3                         |
| Unknown                           | 3  | 0                             | 4                         |
| Race                              |  |                               |                           |
| Units: Subjects                   |  |                               |                           |
| American Indian or Alaskan Native | 0  | 0                             | 0                         |
| Asian                             | 0  | 1                             | 0                         |
| Black or African American         | 3  | 0                             | 2                         |

|  |         |         |         |
|--|---------|---------|---------|
| Native Hawaiian or Other Pacific Islander                    | 0       | 0       | 0       |
| White  | 31      | 17      | 72      |
| Other  | 1       | 0       | 1       |
| Not Reported   | 0       | 0       | 0       |
| Eastern Cooperative Oncology Group Performance Status        |         |         |         |
| Eastern Cooperative Oncology Group (ECOG) Performance Status |         |         |         |
| Units: Subjects  |         |         |         |
| ECOG 0   | 18      | 10      | 33      |
| ECOG 1   | 17      | 8       | 42      |
| Smoking Status   |         |         |         |
| Units: Subjects  |         |         |         |
| Smoker   | 3       | 3       | 23      |
| Past smoker  | 19      | 7       | 46      |
| Non-smoker   | 13      | 8       | 6       |
| Unknown  | 0       | 0       | 0       |
| Height   |         |         |         |
| Units: centimeters   |         |         |         |
| arithmetic mean  | 171.6   | 171.5   | 169.4   |
| standard deviation   | ± 11.94 | ± 11.42 | ± 9.38  |
| Weight   |         |         |         |
| Units: kilograms   |         |         |         |
| arithmetic mean  | 86.7    | 79.2    | 73.6    |
| standard deviation   | ± 17.36 | ± 24.53 | ± 15.87 |
| Calculated Body Mass Index                                   |         |         |         |
| Units: kilogram(s)/square metre                              |         |         |         |
| arithmetic mean  | 29.6    | 26.5    | 25.6    |
| standard deviation   | ± 5.70  | ± 6.18  | ± 5.07  |

| Reporting group values | Cohort 3 (dose expansion) | Cohort 4/5 (dose expansion) | Total |
|------------------------|---------------------------|-----------------------------|-------|
| Number of subjects     | 17                        | 17                          | 162   |
| Age categorical        |                           |                             |       |
| Units: Subjects        |                           |                             |       |
| Adults (18-64 years)   | 6                         | 9                           | 74    |
| From 65-84 years       | 11                        | 8                           | 87    |
| 85 years and over      | 0                         | 0                           | 1     |
| Age continuous         |                           |                             |       |
| Units: years           |                           |                             |       |
| arithmetic mean        | 67.9                      | 61.1                        |       |
| standard deviation     | ± 5.97                    | ± 10.35                     | -     |
| Gender categorical     |                           |                             |       |
| Units: Subjects        |                           |                             |       |
| Female                 | 4                         | 7                           | 57    |
| Male                   | 13                        | 10                          | 105   |
| Ethnicity              |                           |                             |       |
| Units: Subjects        |                           |                             |       |
| Hispanic or Latino     | 0                         | 0                           | 5     |
| Not Hispanic or Latino | 17                        | 14                          | 144   |
| Not Reported           | 0                         | 1                           | 4     |
| Unknown                | 0                         | 2                           | 9     |
| Race                   |                           |                             |       |



|  |         |         |     |
|--|---------|---------|-----|
| Units: Subjects  |         |         |     |
| American Indian or Alaskan Native                            | 0       | 0       | 0   |
| Asian  | 0       | 0       | 1   |
| Black or African American                                    | 1       | 1       | 7   |
| Native Hawaiian or Other Pacific Islander                    | 0       | 0       | 0   |
| White  | 16      | 15      | 151 |
| Other  | 0       | 0       | 2   |
| Not Reported   | 0       | 1       | 1   |
| Eastern Cooperative Oncology Group Performance Status        |         |         |     |
| Eastern Cooperative Oncology Group (ECOG) Performance Status |         |         |     |
| Units: Subjects  |         |         |     |
| ECOG 0   | 8       | 6       | 75  |
| ECOG 1   | 9       | 11      | 87  |
| Smoking Status   |         |         |     |
| Units: Subjects  |         |         |     |
| Smoker   | 3       | 2       | 34  |
| Past smoker  | 11      | 13      | 96  |
| Non-smoker   | 3       | 2       | 32  |
| Unknown  | 0       | 0       | 0   |
| Height   |         |         |     |
| Units: centimeters   |         |         |     |
| arithmetic mean  | 171.3   | 174.5   |     |
| standard deviation   | ± 8.30  | ± 10.64 | -   |
| Weight   |         |         |     |
| Units: kilograms   |         |         |     |
| arithmetic mean  | 74.3    | 78.7    |     |
| standard deviation   | ± 10.10 | ± 16.99 | -   |
| Calculated Body Mass Index                                   |         |         |     |
| Units: kilogram(s)/square metre                              |         |         |     |
| arithmetic mean  | 25.3    | 25.9    |     |
| standard deviation   | ± 2.40  | ± 5.66  | -   |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Cohort 0 (Before Protocol Amendment 5.0) |
| Reporting group description:<br>Patients enrolled before Protocol Amendment 5.0   |  |
| Reporting group title   | Cohort 1a (dose optimization)            |
| Reporting group description:<br>Patients enrolled in the 3 + 3 dose optimization schema (Cohort 1a) were to start NKTR-214 at a dose of 0.008 mg/kg once every 3 weeks (q3w) with pembrolizumab.  |  |
| Reporting group title   | Cohort 2 (dose expansion)                |
| Reporting group description:<br>Patients were to receive a dose of 0.006 mg/kg of NKTR-214 combined with pembrolizumab.   |  |
| Reporting group title   | Cohort 3 (dose expansion)                |
| Reporting group description:<br>Patients were to receive a starting at a dose of 0.010 mg/kg of NKTR-214 combined with pembrolizumab.   |  |
| Reporting group title   | Cohort 4/5 (dose expansion)              |
| Reporting group description:<br>Following review of safety and efficacy data from Cohorts 2 and 3, a decision was to be made to initiate Cohorts 4 and 5. In Cohorts 4 and 5, patients were to receive 0.006 mg/kg of NKTR-214 combined with pembrolizumab and platinum-based chemotherapy. |  |
| Subject analysis set title  | Cohort 1a: NKTR-214 0.008 mg/kg          |
| Subject analysis set type   | Sub-group analysis                       |
| Subject analysis set description:<br>Patients who received NKTR-214 0.008 mg/kg every 3 weeks + pembrolizumab 200 mg in Cohort 1a.  |  |
| Subject analysis set title  | Cohort 1a: NKTR-214 0.010 mg/kg          |
| Subject analysis set type   | Sub-group analysis                       |
| Subject analysis set description:<br>Patients who received NKTR-214 0.010 mg/kg every 3 weeks + pembrolizumab 200 mg in Cohort 1a.  |  |
| Subject analysis set title  | Cohort 1a: NKTR-214 0.012 mg/kg          |
| Subject analysis set type   | Sub-group analysis                       |
| Subject analysis set description:<br>Patients who received NKTR-214 0.012 mg/kg every 3 weeks + pembrolizumab 200 mg in Cohort 1a.  |  |

### Primary: Cohort 2: Objective Response Rate for Dose Expansion Cohorts - Objective Response

|  |   |
|--|---|
| End point title  | Cohort 2: Objective Response Rate for Dose Expansion Cohorts - Objective Response <sup>[1][2]</sup> |
| End point description:<br>Objective Response Rate per blinded independent central review (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) for the Response Evaluable Population dose expansion Cohort 2. The Response Evaluable Population was subjects who received at least 1 dose (or partial dose) of study drug, had measurable disease (per RECIST 1.1) at baseline, and had at least 1 post-baseline assessment of tumor response.<br><br>Objective response is the sum of confirmed complete response and confirmed partial response. |   |
| End point type   | Primary   |
| End point timeframe:<br>Until disease progression, death, unacceptable toxicity, symptomatic deterioration, Investigator's decision to discontinue treatment, patient withdrew consent or was lost to follow-up, or the study was terminated by the Sponsor; or until max 2 years.   |   |

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: Not applicable.

[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: Endpoints are presented by individual cohort.

| End point values            | Cohort 2 (dose expansion) |  |  |  |
|-----------------------------|---------------------------|--|--|--|
| Subject group type          | Reporting group           |  |  |  |
| Number of subjects analysed | 60                        |  |  |  |
| Units: participants         | 13                        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Cohort 3: Objective Response Rate for Dose Expansion Cohorts - Objective Response

|                 |   |
|-----------------|---|
| End point title | Cohort 3: Objective Response Rate for Dose Expansion Cohorts - Objective Response <sup>[3]</sup> <sup>[4]</sup> |
|-----------------|---|

End point description:

Objective Response Rate per blinded independent central review (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) for the Response Evaluable Population dose expansion Cohort 3. The Response Evaluable Population was subjects who received at least 1 dose (or partial dose) of study drug, had measurable disease (per RECIST 1.1) at baseline, and had at least 1 post-baseline assessment of tumor response.

Objective response is the sum of confirmed complete response and confirmed partial response.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Until disease progression, death, unacceptable toxicity, symptomatic deterioration, Investigator's decision to discontinue treatment, patient withdrew consent or was lost to follow-up, or the study was terminated by the Sponsor; or until max 2 years.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not applicable.

[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: Endpoints are presented by individual cohort.

| End point values            | Cohort 3 (dose expansion) |  |  |  |
|-----------------------------|---------------------------|--|--|--|
| Subject group type          | Reporting group           |  |  |  |
| Number of subjects analysed | 13                        |  |  |  |
| Units: participants         | 2                         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### **Primary: Cohort 4+5: Primary Endpoint: Objective Response Rate for Dose Expansion Cohorts - Objective Response**

|                 |   |
|-----------------|---|
| End point title | Cohort 4+5: Primary Endpoint: Objective Response Rate for Dose Expansion Cohorts - Objective Response <sup>[5][6]</sup> |
|-----------------|---|

End point description:

Objective Response Rate per blinded independent central review (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) for the Response Evaluable Population dose expansion Cohorts 4+5. The Response Evaluable Population was subjects who received at least 1 dose (or partial dose) of study drug, had measurable disease (per RECIST 1.1) at baseline, and had at least 1 post-baseline assessment of tumor response.

Objective response is the sum of confirmed complete response and confirmed partial response.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Until disease progression, death, unacceptable toxicity, symptomatic deterioration, Investigator's decision to discontinue treatment, patient withdrew consent or was lost to follow-up, or the study was terminated by the Sponsor; or until max 2 years.

Notes:

[5] - 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: Not applicable.

[6] - 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: Endpoints are presented by individual cohort.

|                             |                                |  |  |  |
|-----------------------------|--------------------------------|--|--|--|
| <b>End point values</b>     | Cohort 4/5<br>(dose expansion) |  |  |  |
| Subject group type          | Reporting group                |  |  |  |
| Number of subjects analysed | 8                              |  |  |  |
| Units: participants         | 2                              |  |  |  |

### **Statistical analyses**

No statistical analyses for this end point

### **Primary: Safety and tolerability of NKTR 214 in combination with pembrolizumab**

|                 |  |
|-----------------|--|
| End point title | Safety and tolerability of NKTR 214 in combination with pembrolizumab <sup>[7]</sup> |
|-----------------|--|

End point description:

To evaluate the safety and tolerability of NKTR 214 in combination with pembrolizumab in Cohort 1a. The overall summary of treatment-emergent adverse events is presented for the Safety Population in dose optimization Cohort 1a.

DLT = dose limiting toxicity

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Screening (Days -28 to -1) to post-treatment period (end of treatment [30 days +/- 10 days after last dose of study medications or before new antineoplastic regimen starts], or long-term follow-up [until withdrawal of consent, death or study termination])

Notes:

[7] - 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: Not applicable.

| <b>End point values</b>              | Cohort 1a:<br>NKTR-214<br>0.008 mg/kg | Cohort 1a:<br>NKTR-214<br>0.010 mg/kg | Cohort 1a:<br>NKTR-214<br>0.012 mg/kg |  |
|--------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--|
| Subject group type                   | Subject analysis set                  | Subject analysis set                  | Subject analysis set                  |  |
| Number of subjects analysed          | 4                                     | 7                                     | 7                                     |  |
| Units: participants                  |                                       |                                       |                                       |  |
| Patients reporting at least 1 DLT    | 0                                     | 1                                     | 0                                     |  |
| DLT: Hypotension (Vascular Disorder) | 0                                     | 1                                     | 0                                     |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Screening (Days -28 to -1) to post-treatment period (end of treatment [30 days +/- 10 days after last dose of study medications or before new antineoplastic regimen starts], or long-term follow-up [until withdrawal of consent, death or study termination])

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

### Dictionary used

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

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

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Before Protocol Amendment 5 |
|-----------------------|-----------------------------|

Reporting group description:

This group presents data for participants enrolled before protocol amendment 5.

|                       |   |
|-----------------------|---|
| Reporting group title | On or after Protocol Amendment 5 (Cohort 1a to 5) |
|-----------------------|---|

Reporting group description:

This group presents data for participants enrolled on or after protocol amendment 5.

| Serious adverse events  | Before Protocol Amendment 5 | On or after Protocol Amendment 5 (Cohort 1a to 5) |  |
|---|-----------------------------|---|--|
| Total subjects affected by serious adverse events                   |                             |   |  |
| subjects affected / exposed   | 19 / 35 (54.29%)            | 56 / 127 (44.09%)                                 |  |
| number of deaths (all causes)                                       | 22                          | 56  |  |
| number of deaths resulting from adverse events                      | 2                           | 5   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |   |  |
| Malignant pleural effusion  |                             |   |  |
| subjects affected / exposed   | 0 / 35 (0.00%)              | 1 / 127 (0.79%)                                   |  |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 1   |  |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0   |  |
| Pericardial effusion malignant                                      |                             |   |  |
| subjects affected / exposed   | 0 / 35 (0.00%)              | 1 / 127 (0.79%)                                   |  |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 1   |  |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0   |  |
| Tumour invasion   |                             |   |  |
| subjects affected / exposed   | 0 / 35 (0.00%)              | 1 / 127 (0.79%)                                   |  |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 2   |  |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0   |  |
| Tumour pain   |                             |   |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Vascular disorders                                   |                |                 |  |
| Hypotension  |                |                 |  |
| subjects affected / exposed                          | 1 / 35 (2.86%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 3 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Deep vein thrombosis                                 |                |                 |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Hypovolaemic shock                                   |                |                 |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Peripheral ischaemia                                 |                |                 |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| General disorders and administration site conditions |                |                 |  |
| Pyrexia  |                |                 |  |
| subjects affected / exposed                          | 1 / 35 (2.86%) | 3 / 127 (2.36%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 1 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Non-cardiac chest pain                               |                |                 |  |
| subjects affected / exposed                          | 1 / 35 (2.86%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all      | 0 / 4          | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Pain   |                |                 |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Chills  |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Fatigue   |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Systemic inflammatory response syndrome         |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Immune system disorders                         |                |                 |  |
| Cytokine release syndrome                       |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Pleural effusion                                |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 4 / 127 (3.15%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Acute respiratory failure                       |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 3 / 127 (2.36%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary embolism                              |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 3 / 127 (2.36%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Respiratory failure                             |                |                 |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 35 (0.00%) | 3 / 127 (2.36%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| Chronic obstructive pulmonary disease           |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dyspnoea  |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hypoxia   |                |                 |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonitis                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumothorax                                    |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary fibrosis                              |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Psychiatric disorders                           |                |                 |  |
| Confusional state                               |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Disorientation                                  |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                           | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all       | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0           |  |
| <b>Investigations</b>                                 |                |                 |  |
| Alanine aminotransferase increased                    |                |                 |  |
| subjects affected / exposed                           | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all       | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0           |  |
| Blood creatine phosphokinase increased                |                |                 |  |
| subjects affected / exposed                           | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all       | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0           |  |
| <b>Injury, poisoning and procedural complications</b> |                |                 |  |
| Infusion related reaction                             |                |                 |  |
| subjects affected / exposed                           | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all       | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0           |  |
| Toxicity to various agents                            |                |                 |  |
| subjects affected / exposed                           | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0           |  |
| <b>Cardiac disorders</b>                              |                |                 |  |
| Atrial fibrillation                                   |                |                 |  |
| subjects affected / exposed                           | 1 / 35 (2.86%) | 4 / 127 (3.15%) |  |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 6           |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0           |  |
| Acute myocardial infarction                           |                |                 |  |
| subjects affected / exposed                           | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0           |  |
| Angina pectoris                                       |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Atrioventricular block complete                 |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Bundle branch block                             |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac arrest                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           |  |
| Cardiac tamponade                               |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Myocarditis                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pericardial effusion                            |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nervous system disorders                        |                |                 |  |
| Embololic stroke                                |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Myasthenic syndrome                             |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| Cerebrovascular accident                        |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Embolic cerebral infarction                     |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Ischaemic stroke                                |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Seizure   |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Spinal cord compression                         |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Toxic encephalopathy                            |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Transient ischaemic attack                      |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Blood and lymphatic system disorders            |                |                 |  |
| Anaemia   |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Eye disorders                                   |                |                 |  |
| Retinal artery occlusion                        |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Diarrhoea                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Colitis ischaemic                               |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dysphagia                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haematemesis                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Intestinal perforation                          |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Large intestinal obstruction                    |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Stomatitis                                      |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hepatobiliary disorders                         |                |                 |  |
| Hepatic failure                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                |                 |  |
| Pruritus  |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Rash  |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Rash maculo-papular                             |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Subcutaneous emphysema                          |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Renal and urinary disorders                     |                |                 |  |
| Acute kidney injury                             |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Obstructive uropathy                            |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Tubulointerstitial nephritis                    |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Back pain                                       |                |                 |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Arthralgia                                      |                |                 |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Bone pain                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal pain                            |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Myalgia   |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Pneumonia                                       |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 7 / 127 (5.51%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 3 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Sepsis  |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Urinary tract infection                         |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Septic shock                                    |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 1           |  |
| Clostridium difficile colitis                   |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cystitis  |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Device related sepsis                           |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Endocarditis                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Lung infection                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory tract infection                     |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Urosepsis                                       |                |                 |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| <b>Metabolism and nutrition disorders</b>       |                |                 |  |
| Dehydration                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 3 / 127 (2.36%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hypercalcaemia                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Diabetic ketoacidosis                           |                |                 |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hypocalcaemia                                   |                |                 |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>  | Before Protocol Amendment 5 | On or after Protocol Amendment 5 (Cohort 1a to 5) |  |
|--|-----------------------------|---|--|
| Total subjects affected by non-serious adverse events                      |                             |   |  |
| subjects affected / exposed  | 35 / 35 (100.00%)           | 124 / 127 (97.64%)                                |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                             |   |  |
| Tumour pain  |                             |   |  |
| subjects affected / exposed  | 1 / 35 (2.86%)              | 2 / 127 (1.57%)                                   |  |
| occurrences (all)  | 1                           | 2   |  |
| Cancer pain  |                             |   |  |
| subjects affected / exposed  | 0 / 35 (0.00%)              | 1 / 127 (0.79%)                                   |  |
| occurrences (all)  | 0                           | 1   |  |
| Lung neoplasm malignant  |                             |   |  |

|                                 |                |                   |  |
|---------------------------------|----------------|-------------------|--|
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 0              | 1                 |  |
| Melanocytic naevus              |                |                   |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 0              | 1                 |  |
| Squamous cell carcinoma of skin |                |                   |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 0              | 1                 |  |
| Vascular disorders              |                |                   |  |
| Hypotension                     |                |                   |  |
| subjects affected / exposed     | 3 / 35 (8.57%) | 18 / 127 (14.17%) |  |
| occurrences (all)               | 3              | 23                |  |
| Hypertension                    |                |                   |  |
| subjects affected / exposed     | 2 / 35 (5.71%) | 10 / 127 (7.87%)  |  |
| occurrences (all)               | 4              | 11                |  |
| Hot flush                       |                |                   |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 4 / 127 (3.15%)   |  |
| occurrences (all)               | 0              | 4                 |  |
| Embolism                        |                |                   |  |
| subjects affected / exposed     | 1 / 35 (2.86%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 1              | 1                 |  |
| Flushing                        |                |                   |  |
| subjects affected / exposed     | 1 / 35 (2.86%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 1              | 1                 |  |
| Lymphoedema                     |                |                   |  |
| subjects affected / exposed     | 1 / 35 (2.86%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 1              | 1                 |  |
| Arterial thrombosis             |                |                   |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 0              | 1                 |  |
| Deep vein thrombosis            |                |                   |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 0              | 1                 |  |
| Peripheral coldness             |                |                   |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)               | 0              | 1                 |  |

|  |                  |                   |  |
|--|------------------|-------------------|--|
| Phlebitis  |                  |                   |  |
| subjects affected / exposed                          | 0 / 35 (0.00%)   | 1 / 127 (0.79%)   |  |
| occurrences (all)                                    | 0                | 1                 |  |
| superior vena  |                  |                   |  |
| subjects affected / exposed                          | 0 / 35 (0.00%)   | 1 / 127 (0.79%)   |  |
| occurrences (all)                                    | 0                | 1                 |  |
| Surgical and medical procedures                      |                  |                   |  |
| Sinus operation                                      |                  |                   |  |
| subjects affected / exposed                          | 0 / 35 (0.00%)   | 1 / 127 (0.79%)   |  |
| occurrences (all)                                    | 0                | 1                 |  |
| General disorders and administration site conditions |                  |                   |  |
| Pyrexia  |                  |                   |  |
| subjects affected / exposed                          | 10 / 35 (28.57%) | 53 / 127 (41.73%) |  |
| occurrences (all)                                    | 18               | 80                |  |
| Fatigue  |                  |                   |  |
| subjects affected / exposed                          | 20 / 35 (57.14%) | 42 / 127 (33.07%) |  |
| occurrences (all)                                    | 24               | 52                |  |
| Chills   |                  |                   |  |
| subjects affected / exposed                          | 6 / 35 (17.14%)  | 27 / 127 (21.26%) |  |
| occurrences (all)                                    | 10               | 34                |  |
| Asthenia   |                  |                   |  |
| subjects affected / exposed                          | 3 / 35 (8.57%)   | 28 / 127 (22.05%) |  |
| occurrences (all)                                    | 3                | 38                |  |
| Influenza like illness                               |                  |                   |  |
| subjects affected / exposed                          | 7 / 35 (20.00%)  | 20 / 127 (15.75%) |  |
| occurrences (all)                                    | 10               | 48                |  |
| Oedema peripheral                                    |                  |                   |  |
| subjects affected / exposed                          | 9 / 35 (25.71%)  | 17 / 127 (13.39%) |  |
| occurrences (all)                                    | 9                | 24                |  |
| Non-cardiac chest pain                               |                  |                   |  |
| subjects affected / exposed                          | 2 / 35 (5.71%)   | 7 / 127 (5.51%)   |  |
| occurrences (all)                                    | 2                | 9                 |  |
| Gait disturbance                                     |                  |                   |  |
| subjects affected / exposed                          | 2 / 35 (5.71%)   | 2 / 127 (1.57%)   |  |
| occurrences (all)                                    | 2                | 2                 |  |
| Malaise  |                  |                   |  |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 127 (0.79%) |
| occurrences (all)           | 14             | 1               |
| Mucosal inflammation        |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 4 / 127 (3.15%) |
| occurrences (all)           | 0              | 4               |
| Catheter site pain          |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 3 / 127 (2.36%) |
| occurrences (all)           | 0              | 3               |
| Face oedema                 |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 127 (1.57%) |
| occurrences (all)           | 1              | 3               |
| Pain                        |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 127 (1.57%) |
| occurrences (all)           | 1              | 2               |
| Localised oedema            |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)           | 0              | 3               |
| Axillary pain               |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 1              | 0               |
| Chest discomfort            |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Chest pain                  |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Device occlusion            |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 4               |
| Feeling abnormal            |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Infusion site extravasation |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 1              | 0               |
| Oedema                      |                |                 |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)  | 1 / 35 (2.86%)<br>1 | 0 / 127 (0.00%)<br>0 |  |
| Puncture site pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Secretion discharge<br>subjects affected / exposed<br>occurrences (all)  | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Systemic inflammatory response<br>syndrome<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 35 (2.86%)<br>1 | 0 / 127 (0.00%)<br>0 |  |
| Immune system disorders<br>Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)           | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)   | 1 / 35 (2.86%)<br>1 | 0 / 127 (0.00%)<br>0 |  |
| Multiple allergies<br>subjects affected / exposed<br>occurrences (all)   | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Reproductive system and breast<br>disorders<br>Pelvic pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 35 (0.00%)<br>0 | 2 / 127 (1.57%)<br>2 |  |
| Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Breast pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 35 (2.86%)<br>1 | 0 / 127 (0.00%)<br>0 |  |
| Erectile dysfunction   |                     |                      |  |

|   |                 |                   |  |
|---|-----------------|-------------------|--|
| subjects affected / exposed                     | 1 / 35 (2.86%)  | 0 / 127 (0.00%)   |  |
| occurrences (all)                               | 1               | 0                 |  |
| Penile pain                                     |                 |                   |  |
| subjects affected / exposed                     | 1 / 35 (2.86%)  | 0 / 127 (0.00%)   |  |
| occurrences (all)                               | 1               | 0                 |  |
| Vaginal haemorrhage                             |                 |                   |  |
| subjects affected / exposed                     | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                               | 0               | 1                 |  |
| Respiratory, thoracic and mediastinal disorders |                 |                   |  |
| Cough   |                 |                   |  |
| subjects affected / exposed                     | 7 / 35 (20.00%) | 30 / 127 (23.62%) |  |
| occurrences (all)                               | 8               | 31                |  |
| Dyspnoea  |                 |                   |  |
| subjects affected / exposed                     | 6 / 35 (17.14%) | 22 / 127 (17.32%) |  |
| occurrences (all)                               | 6               | 26                |  |
| Nasal congestion                                |                 |                   |  |
| subjects affected / exposed                     | 3 / 35 (8.57%)  | 7 / 127 (5.51%)   |  |
| occurrences (all)                               | 4               | 13                |  |
| Rhinorrhoea                                     |                 |                   |  |
| subjects affected / exposed                     | 0 / 35 (0.00%)  | 5 / 127 (3.94%)   |  |
| occurrences (all)                               | 0               | 6                 |  |
| Dysphonia                                       |                 |                   |  |
| subjects affected / exposed                     | 2 / 35 (5.71%)  | 2 / 127 (1.57%)   |  |
| occurrences (all)                               | 2               | 2                 |  |
| Dyspnoea exertional                             |                 |                   |  |
| subjects affected / exposed                     | 0 / 35 (0.00%)  | 4 / 127 (3.15%)   |  |
| occurrences (all)                               | 0               | 4                 |  |
| Hypoxia   |                 |                   |  |
| subjects affected / exposed                     | 0 / 35 (0.00%)  | 4 / 127 (3.15%)   |  |
| occurrences (all)                               | 0               | 4                 |  |
| Oropharyngeal pain                              |                 |                   |  |
| subjects affected / exposed                     | 3 / 35 (8.57%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                               | 3               | 1                 |  |
| Pulmonary embolism                              |                 |                   |  |

|  |                |                 |
|--|----------------|-----------------|
| subjects affected / exposed                        | 0 / 35 (0.00%) | 4 / 127 (3.15%) |
| occurrences (all)                                  | 0              | 4               |
| Haemoptysis  |                |                 |
| subjects affected / exposed                        | 1 / 35 (2.86%) | 2 / 127 (1.57%) |
| occurrences (all)                                  | 1              | 2               |
| Pleural effusion                                   |                |                 |
| subjects affected / exposed                        | 0 / 35 (0.00%) | 3 / 127 (2.36%) |
| occurrences (all)                                  | 0              | 3               |
| Upper-airway cough syndrome                        |                |                 |
| subjects affected / exposed                        | 0 / 35 (0.00%) | 3 / 127 (2.36%) |
| occurrences (all)                                  | 0              | 3               |
| Wheezing   |                |                 |
| subjects affected / exposed                        | 3 / 35 (8.57%) | 0 / 127 (0.00%) |
| occurrences (all)                                  | 3              | 0               |
| Hiccups  |                |                 |
| subjects affected / exposed                        | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                                  | 0              | 2               |
| Laryngeal haemorrhage                              |                |                 |
| subjects affected / exposed                        | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)                                  | 2              | 1               |
| Acute respiratory failure                          |                |                 |
| subjects affected / exposed                        | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                                  | 0              | 1               |
| Bronchial secretion retention                      |                |                 |
| subjects affected / exposed                        | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                                  | 0              | 1               |
| Epistaxis  |                |                 |
| subjects affected / exposed                        | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                                  | 0              | 1               |
| Increased viscosity of upper respiratory secretion |                |                 |
| subjects affected / exposed                        | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                                  | 0              | 1               |
| Laryngeal oedema                                   |                |                 |
| subjects affected / exposed                        | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)                                  | 1              | 0               |

|                             |                |                  |  |
|-----------------------------|----------------|------------------|--|
| Lung infiltration           |                |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0              | 1                |  |
| Orthopnoea                  |                |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0              | 1                |  |
| Pharyngeal erythema         |                |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0              | 1                |  |
| Pleural fibrosis            |                |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0              | 1                |  |
| Pleuritic pain              |                |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0              | 1                |  |
| Pneumothorax                |                |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0              | 1                |  |
| Productive cough            |                |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0              | 1                |  |
| Pulmonary hypertension      |                |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 1              | 0                |  |
| Rhinitis allergic           |                |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0              | 1                |  |
| Tachypnoea                  |                |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 1              | 0                |  |
| Psychiatric disorders       |                |                  |  |
| Insomnia                    |                |                  |  |
| subjects affected / exposed | 2 / 35 (5.71%) | 10 / 127 (7.87%) |  |
| occurrences (all)           | 2              | 10               |  |
| Anxiety                     |                |                  |  |



|                                      |                 |                   |  |
|--------------------------------------|-----------------|-------------------|--|
| subjects affected / exposed          | 4 / 35 (11.43%) | 7 / 127 (5.51%)   |  |
| occurrences (all)                    | 4               | 7                 |  |
| Depression                           |                 |                   |  |
| subjects affected / exposed          | 3 / 35 (8.57%)  | 3 / 127 (2.36%)   |  |
| occurrences (all)                    | 3               | 3                 |  |
| Confusional state                    |                 |                   |  |
| subjects affected / exposed          | 2 / 35 (5.71%)  | 3 / 127 (2.36%)   |  |
| occurrences (all)                    | 3               | 3                 |  |
| Restlessness                         |                 |                   |  |
| subjects affected / exposed          | 1 / 35 (2.86%)  | 2 / 127 (1.57%)   |  |
| occurrences (all)                    | 1               | 2                 |  |
| Depressed mood                       |                 |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%)  | 2 / 127 (1.57%)   |  |
| occurrences (all)                    | 0               | 2                 |  |
| Hallucination                        |                 |                   |  |
| subjects affected / exposed          | 1 / 35 (2.86%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                    | 1               | 1                 |  |
| Sleep disorder                       |                 |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%)  | 2 / 127 (1.57%)   |  |
| occurrences (all)                    | 0               | 2                 |  |
| Agitation                            |                 |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                    | 0               | 1                 |  |
| Delirium                             |                 |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                    | 0               | 1                 |  |
| Disorientation                       |                 |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                    | 0               | 2                 |  |
| Investigations                       |                 |                   |  |
| Weight decreased                     |                 |                   |  |
| subjects affected / exposed          | 4 / 35 (11.43%) | 22 / 127 (17.32%) |  |
| occurrences (all)                    | 4               | 28                |  |
| Aspartate aminotransferase increased |                 |                   |  |

|  |                 |                   |
|--|-----------------|-------------------|
| subjects affected / exposed              | 1 / 35 (2.86%)  | 21 / 127 (16.54%) |
| occurrences (all)                        | 1               | 21                |
| Alanine aminotransferase increased       |                 |                   |
| subjects affected / exposed              | 1 / 35 (2.86%)  | 18 / 127 (14.17%) |
| occurrences (all)                        | 1               | 19                |
| Blood creatinine increased               |                 |                   |
| subjects affected / exposed              | 6 / 35 (17.14%) | 9 / 127 (7.09%)   |
| occurrences (all)                        | 9               | 10                |
| Lymphocyte count decreased               |                 |                   |
| subjects affected / exposed              | 0 / 35 (0.00%)  | 10 / 127 (7.87%)  |
| occurrences (all)                        | 0               | 10                |
| Gamma-glutamyltransferase increased      |                 |                   |
| subjects affected / exposed              | 1 / 35 (2.86%)  | 7 / 127 (5.51%)   |
| occurrences (all)                        | 1               | 7                 |
| Amylase increased                        |                 |                   |
| subjects affected / exposed              | 1 / 35 (2.86%)  | 6 / 127 (4.72%)   |
| occurrences (all)                        | 1               | 7                 |
| Blood alkaline phosphatase increased     |                 |                   |
| subjects affected / exposed              | 1 / 35 (2.86%)  | 4 / 127 (3.15%)   |
| occurrences (all)                        | 1               | 4                 |
| Blood creatine phosphokinase increased   |                 |                   |
| subjects affected / exposed              | 1 / 35 (2.86%)  | 4 / 127 (3.15%)   |
| occurrences (all)                        | 1               | 4                 |
| Eosinophil count increased               |                 |                   |
| subjects affected / exposed              | 0 / 35 (0.00%)  | 5 / 127 (3.94%)   |
| occurrences (all)                        | 0               | 5                 |
| Lipase increased                         |                 |                   |
| subjects affected / exposed              | 2 / 35 (5.71%)  | 3 / 127 (2.36%)   |
| occurrences (all)                        | 2               | 4                 |
| Blood bilirubin increased                |                 |                   |
| subjects affected / exposed              | 0 / 35 (0.00%)  | 3 / 127 (2.36%)   |
| occurrences (all)                        | 0               | 3                 |
| International normalised ratio increased |                 |                   |

|                                       |                |                 |
|---------------------------------------|----------------|-----------------|
| subjects affected / exposed           | 1 / 35 (2.86%) | 2 / 127 (1.57%) |
| occurrences (all)                     | 1              | 2               |
| Neutrophil count decreased            |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 3 / 127 (2.36%) |
| occurrences (all)                     | 0              | 4               |
| Platelet count decreased              |                |                 |
| subjects affected / exposed           | 1 / 35 (2.86%) | 2 / 127 (1.57%) |
| occurrences (all)                     | 1              | 3               |
| Weight increased                      |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 3 / 127 (2.36%) |
| occurrences (all)                     | 0              | 4               |
| Blood albumin decreased               |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                     | 0              | 2               |
| Blood lactate dehydrogenase increased |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                     | 0              | 2               |
| Troponin I increased                  |                |                 |
| subjects affected / exposed           | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)                     | 1              | 1               |
| Troponin increased                    |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                     | 0              | 2               |
| White blood cell count increased      |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                     | 0              | 2               |
| Blood calcium increased               |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                     | 0              | 1               |
| Blood creatine increased              |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                     | 0              | 1               |
| Blood creatine phosphokinase MB       |                |                 |
| subjects affected / exposed           | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                     | 0              | 1               |

|   |                     |                      |  |
|---|---------------------|----------------------|--|
| Blood folate decreased<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Blood sodium decreased<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 35 (2.86%)<br>2 | 0 / 127 (0.00%)<br>0 |  |
| Blood thyroid stimulating hormone decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Brain natriuretic peptide increased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)                | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Clostridium test positive<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)              | 1 / 35 (2.86%)<br>1 | 0 / 127 (0.00%)<br>0 |  |
| Glomerular filtration rate decreased<br>subjects affected / exposed<br>occurrences (all)        | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Neutrophil count increased  |                     |                      |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Injury, poisoning and procedural complications                                       |                     |                      |  |
| Fall   |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 2 / 35 (5.71%)<br>4 | 6 / 127 (4.72%)<br>7 |  |
| Hand fracture  |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Infusion related reaction  |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Procedural pain  |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Thermal burn   |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Vaccination complication   |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Vascular access complication   |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Cardiac disorders  |                     |                      |  |
| Tachycardia  |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 35 (2.86%)<br>1 | 5 / 127 (3.94%)<br>5 |  |
| Sinus tachycardia  |                     |                      |  |
| subjects affected / exposed<br>occurrences (all)                                     | 2 / 35 (5.71%)<br>2 | 1 / 127 (0.79%)<br>2 |  |
| Atrial fibrillation  |                     |                      |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 1 / 35 (2.86%)   | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 1                | 1                |  |
| Palpitations                |                  |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%)   | 2 / 127 (1.57%)  |  |
| occurrences (all)           | 0                | 2                |  |
| Pericardial effusion        |                  |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)   | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 1                | 1                |  |
| Cardiac failure congestive  |                  |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)   | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 1                | 0                |  |
| Nervous system disorders    |                  |                  |  |
| Dizziness                   |                  |                  |  |
| subjects affected / exposed | 10 / 35 (28.57%) | 10 / 127 (7.87%) |  |
| occurrences (all)           | 11               | 11               |  |
| Headache                    |                  |                  |  |
| subjects affected / exposed | 6 / 35 (17.14%)  | 12 / 127 (9.45%) |  |
| occurrences (all)           | 11               | 14               |  |
| Neuropathy peripheral       |                  |                  |  |
| subjects affected / exposed | 2 / 35 (5.71%)   | 4 / 127 (3.15%)  |  |
| occurrences (all)           | 2                | 4                |  |
| Dysgeusia                   |                  |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)   | 4 / 127 (3.15%)  |  |
| occurrences (all)           | 1                | 4                |  |
| Paraesthesia                |                  |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)   | 3 / 127 (2.36%)  |  |
| occurrences (all)           | 1                | 4                |  |
| Syncope                     |                  |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%)   | 4 / 127 (3.15%)  |  |
| occurrences (all)           | 0                | 4                |  |
| Cognitive disorder          |                  |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)   | 2 / 127 (1.57%)  |  |
| occurrences (all)           | 1                | 2                |  |
| Sinus headache              |                  |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)   | 2 / 127 (1.57%)  |  |
| occurrences (all)           | 1                | 2                |  |

|                               |                |                 |
|-------------------------------|----------------|-----------------|
| Tremor                        |                |                 |
| subjects affected / exposed   | 1 / 35 (2.86%) | 2 / 127 (1.57%) |
| occurrences (all)             | 1              | 2               |
| Ataxia                        |                |                 |
| subjects affected / exposed   | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)             | 0              | 2               |
| Peripheral sensory neuropathy |                |                 |
| subjects affected / exposed   | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)             | 2              | 1               |
| Burning sensation             |                |                 |
| subjects affected / exposed   | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)             | 0              | 1               |
| Carotid artery stenosis       |                |                 |
| subjects affected / exposed   | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)             | 0              | 1               |
| Carpal tunnel syndrome        |                |                 |
| subjects affected / exposed   | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)             | 0              | 1               |
| Disturbance in attention      |                |                 |
| subjects affected / exposed   | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)             | 1              | 0               |
| Dyskinesia                    |                |                 |
| subjects affected / exposed   | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)             | 1              | 0               |
| Hyperaesthesia                |                |                 |
| subjects affected / exposed   | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)             | 1              | 0               |
| Hypersomnia                   |                |                 |
| subjects affected / exposed   | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)             | 0              | 1               |
| Hypoaesthesia                 |                |                 |
| subjects affected / exposed   | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)             | 0              | 1               |
| Hypotonia                     |                |                 |
| subjects affected / exposed   | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)             | 0              | 1               |

|                                      |                |                   |  |
|--------------------------------------|----------------|-------------------|--|
| Migraine                             |                |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)                    | 0              | 1                 |  |
| Restless legs syndrome               |                |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)                    | 0              | 1                 |  |
| Somnolence                           |                |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)                    | 0              | 1                 |  |
| Vasogenic cerebral oedema            |                |                   |  |
| subjects affected / exposed          | 1 / 35 (2.86%) | 0 / 127 (0.00%)   |  |
| occurrences (all)                    | 1              | 0                 |  |
| Visual field defect                  |                |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%) | 1 / 127 (0.79%)   |  |
| occurrences (all)                    | 0              | 1                 |  |
| Blood and lymphatic system disorders |                |                   |  |
| Anaemia                              |                |                   |  |
| subjects affected / exposed          | 3 / 35 (8.57%) | 20 / 127 (15.75%) |  |
| occurrences (all)                    | 3              | 31                |  |
| Eosinophilia                         |                |                   |  |
| subjects affected / exposed          | 2 / 35 (5.71%) | 8 / 127 (6.30%)   |  |
| occurrences (all)                    | 3              | 11                |  |
| Leukocytosis                         |                |                   |  |
| subjects affected / exposed          | 1 / 35 (2.86%) | 2 / 127 (1.57%)   |  |
| occurrences (all)                    | 1              | 2                 |  |
| Neutropenia                          |                |                   |  |
| subjects affected / exposed          | 1 / 35 (2.86%) | 2 / 127 (1.57%)   |  |
| occurrences (all)                    | 1              | 2                 |  |
| Lymph node pain                      |                |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%) | 2 / 127 (1.57%)   |  |
| occurrences (all)                    | 0              | 2                 |  |
| Lymphadenopathy                      |                |                   |  |
| subjects affected / exposed          | 0 / 35 (0.00%) | 2 / 127 (1.57%)   |  |
| occurrences (all)                    | 0              | 2                 |  |
| Thrombocytopenia                     |                |                   |  |



|                                 |                |                 |  |
|---------------------------------|----------------|-----------------|--|
| subjects affected / exposed     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences (all)               | 0              | 2               |  |
| Anaemia of malignant disease    |                |                 |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences (all)               | 0              | 1               |  |
| Haemolytic anaemia              |                |                 |  |
| subjects affected / exposed     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences (all)               | 1              | 0               |  |
| Iron deficiency anaemia         |                |                 |  |
| subjects affected / exposed     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences (all)               | 1              | 0               |  |
| Leukopenia                      |                |                 |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences (all)               | 0              | 1               |  |
| Lymphopenia                     |                |                 |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences (all)               | 0              | 1               |  |
| Normochromic normocytic anaemia |                |                 |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences (all)               | 0              | 1               |  |
| Ear and labyrinth disorders     |                |                 |  |
| Hearing impaired                |                |                 |  |
| subjects affected / exposed     | 0 / 35 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences (all)               | 0              | 2               |  |
| Tinnitus                        |                |                 |  |
| subjects affected / exposed     | 1 / 35 (2.86%) | 1 / 127 (0.79%) |  |
| occurrences (all)               | 1              | 1               |  |
| Deafness                        |                |                 |  |
| subjects affected / exposed     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences (all)               | 1              | 0               |  |
| Deafness bilateral              |                |                 |  |
| subjects affected / exposed     | 1 / 35 (2.86%) | 0 / 127 (0.00%) |  |
| occurrences (all)               | 1              | 0               |  |
| Eye disorders                   |                |                 |  |
| Eye swelling                    |                |                 |  |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 127 (1.57%) |
| occurrences (all)           | 3              | 3               |
| Vision blurred              |                |                 |
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 127 (1.57%) |
| occurrences (all)           | 2              | 2               |
| Dry eye                     |                |                 |
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 127 (0.79%) |
| occurrences (all)           | 2              | 1               |
| Eyelid oedema               |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)           | 0              | 3               |
| Periorbital oedema          |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)           | 2              | 2               |
| Uveitis                     |                |                 |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 127 (0.00%) |
| occurrences (all)           | 2              | 0               |
| Blepharitis                 |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Erythema of eyelid          |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Eye pain                    |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 2               |
| Keratitis                   |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Lacrimation increased       |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Meibomian gland dysfunction |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Metamorphopsia              |                |                 |

|                             |                  |                   |  |
|-----------------------------|------------------|-------------------|--|
| subjects affected / exposed | 0 / 35 (0.00%)   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0                | 1                 |  |
| Parophthalmia               |                  |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0                | 1                 |  |
| Visual acuity reduced       |                  |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0                | 1                 |  |
| Vitreous floaters           |                  |                   |  |
| subjects affected / exposed | 1 / 35 (2.86%)   | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1                | 0                 |  |
| Vitreous haemorrhage        |                  |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0                | 1                 |  |
| Gastrointestinal disorders  |                  |                   |  |
| Nausea                      |                  |                   |  |
| subjects affected / exposed | 14 / 35 (40.00%) | 46 / 127 (36.22%) |  |
| occurrences (all)           | 18               | 74                |  |
| Diarrhoea                   |                  |                   |  |
| subjects affected / exposed | 11 / 35 (31.43%) | 35 / 127 (27.56%) |  |
| occurrences (all)           | 24               | 46                |  |
| Vomiting                    |                  |                   |  |
| subjects affected / exposed | 11 / 35 (31.43%) | 27 / 127 (21.26%) |  |
| occurrences (all)           | 12               | 43                |  |
| Constipation                |                  |                   |  |
| subjects affected / exposed | 3 / 35 (8.57%)   | 16 / 127 (12.60%) |  |
| occurrences (all)           | 3                | 20                |  |
| Abdominal pain              |                  |                   |  |
| subjects affected / exposed | 3 / 35 (8.57%)   | 7 / 127 (5.51%)   |  |
| occurrences (all)           | 4                | 7                 |  |
| Dry mouth                   |                  |                   |  |
| subjects affected / exposed | 4 / 35 (11.43%)  | 6 / 127 (4.72%)   |  |
| occurrences (all)           | 4                | 6                 |  |
| Dysphagia                   |                  |                   |  |
| subjects affected / exposed | 3 / 35 (8.57%)   | 6 / 127 (4.72%)   |  |
| occurrences (all)           | 3                | 6                 |  |

|                                  |                |                 |
|----------------------------------|----------------|-----------------|
| Stomatitis                       |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 7 / 127 (5.51%) |
| occurrences (all)                | 1              | 7               |
| Dyspepsia                        |                |                 |
| subjects affected / exposed      | 2 / 35 (5.71%) | 5 / 127 (3.94%) |
| occurrences (all)                | 2              | 5               |
| Abdominal pain upper             |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 4 / 127 (3.15%) |
| occurrences (all)                | 1              | 4               |
| Gastrooesophageal reflux disease |                |                 |
| subjects affected / exposed      | 3 / 35 (8.57%) | 1 / 127 (0.79%) |
| occurrences (all)                | 3              | 1               |
| Colitis                          |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                | 0              | 2               |
| Flatulence                       |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)                | 1              | 1               |
| Gastritis                        |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                | 0              | 2               |
| Glossodynia                      |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)                | 1              | 1               |
| Lip swelling                     |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)                | 1              | 1               |
| Toothache                        |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                | 0              | 2               |
| Abdominal discomfort             |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)                | 1              | 0               |
| Abdominal distension             |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                | 0              | 1               |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| Abdominal hernia            |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Abdominal pain lower        |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 3              | 0               |
| Anal haemorrhage            |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Aphthous ulcer              |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Dental caries               |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Gastric ulcer               |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 1              | 0               |
| Gastrointestinal disorder   |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Gingival pain               |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Haemorrhoidal haemorrhage   |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Mouth ulceration            |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Oesophagitis                |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Oral discomfort             |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 5               |

|  |                 |                   |  |
|--|-----------------|-------------------|--|
| Oral pain                              |                 |                   |  |
| subjects affected / exposed            | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                      | 0               | 1                 |  |
| Rectal haemorrhage                     |                 |                   |  |
| subjects affected / exposed            | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                      | 0               | 1                 |  |
| Rectal tenesmus                        |                 |                   |  |
| subjects affected / exposed            | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                      | 0               | 1                 |  |
| Reflux gastritis                       |                 |                   |  |
| subjects affected / exposed            | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                      | 0               | 1                 |  |
| Upper gastrointestinal haemorrhage     |                 |                   |  |
| subjects affected / exposed            | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                      | 0               | 1                 |  |
| Hepatobiliary disorders                |                 |                   |  |
| Cholelithiasis                         |                 |                   |  |
| subjects affected / exposed            | 1 / 35 (2.86%)  | 0 / 127 (0.00%)   |  |
| occurrences (all)                      | 1               | 0                 |  |
| Hepatitis acute                        |                 |                   |  |
| subjects affected / exposed            | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                      | 0               | 1                 |  |
| Liver disorder                         |                 |                   |  |
| subjects affected / exposed            | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)                      | 0               | 1                 |  |
| Skin and subcutaneous tissue disorders |                 |                   |  |
| Pruritus                               |                 |                   |  |
| subjects affected / exposed            | 8 / 35 (22.86%) | 28 / 127 (22.05%) |  |
| occurrences (all)                      | 10              | 36                |  |
| Rash                                   |                 |                   |  |
| subjects affected / exposed            | 4 / 35 (11.43%) | 24 / 127 (18.90%) |  |
| occurrences (all)                      | 4               | 26                |  |
| Rash maculo-papular                    |                 |                   |  |
| subjects affected / exposed            | 5 / 35 (14.29%) | 13 / 127 (10.24%) |  |
| occurrences (all)                      | 5               | 20                |  |
| Dry skin                               |                 |                   |  |

|   |                |                   |
|---|----------------|-------------------|
| subjects affected / exposed                 | 2 / 35 (5.71%) | 13 / 127 (10.24%) |
| occurrences (all)                           | 2              | 14                |
| Urticaria                                   |                |                   |
| subjects affected / exposed                 | 0 / 35 (0.00%) | 5 / 127 (3.94%)   |
| occurrences (all)                           | 0              | 8                 |
| Night sweats                                |                |                   |
| subjects affected / exposed                 | 2 / 35 (5.71%) | 2 / 127 (1.57%)   |
| occurrences (all)                           | 2              | 2                 |
| Alopecia                                    |                |                   |
| subjects affected / exposed                 | 1 / 35 (2.86%) | 2 / 127 (1.57%)   |
| occurrences (all)                           | 1              | 2                 |
| Erythema                                    |                |                   |
| subjects affected / exposed                 | 2 / 35 (5.71%) | 1 / 127 (0.79%)   |
| occurrences (all)                           | 2              | 3                 |
| Hyperhidrosis                               |                |                   |
| subjects affected / exposed                 | 0 / 35 (0.00%) | 3 / 127 (2.36%)   |
| occurrences (all)                           | 0              | 3                 |
| Rash erythematous                           |                |                   |
| subjects affected / exposed                 | 2 / 35 (5.71%) | 1 / 127 (0.79%)   |
| occurrences (all)                           | 2              | 1                 |
| Skin lesion                                 |                |                   |
| subjects affected / exposed                 | 0 / 35 (0.00%) | 3 / 127 (2.36%)   |
| occurrences (all)                           | 0              | 3                 |
| Dermatitis                                  |                |                   |
| subjects affected / exposed                 | 0 / 35 (0.00%) | 2 / 127 (1.57%)   |
| occurrences (all)                           | 0              | 2                 |
| Dermatitis acneiform                        |                |                   |
| subjects affected / exposed                 | 0 / 35 (0.00%) | 2 / 127 (1.57%)   |
| occurrences (all)                           | 0              | 2                 |
| Dermatitis allergic                         |                |                   |
| subjects affected / exposed                 | 0 / 35 (0.00%) | 2 / 127 (1.57%)   |
| occurrences (all)                           | 0              | 2                 |
| Palmar-plantar erythrodysaesthesia syndrome |                |                   |
| subjects affected / exposed                 | 0 / 35 (0.00%) | 2 / 127 (1.57%)   |
| occurrences (all)                           | 0              | 2                 |

|                                  |                |                 |
|----------------------------------|----------------|-----------------|
| Rash papular                     |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                | 0              | 2               |
| Rash pruritic                    |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)                | 2              | 1               |
| Skin exfoliation                 |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                | 0              | 2               |
| Blood blister                    |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)                | 1              | 0               |
| Decubitus ulcer                  |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                | 0              | 1               |
| Dermatitis bullous               |                |                 |
| subjects affected / exposed      | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)                | 1              | 0               |
| Drug eruption                    |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                | 0              | 1               |
| Hyperkeratosis                   |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                | 0              | 1               |
| Keratolysis exfoliativa acquired |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                | 0              | 1               |
| Onycholysis                      |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                | 0              | 1               |
| Prurigo                          |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                | 0              | 1               |
| Skin fissures                    |                |                 |
| subjects affected / exposed      | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                | 0              | 1               |



|  |                     |                      |  |
|--|---------------------|----------------------|--|
| Skin induration<br>subjects affected / exposed<br>occurrences (all)        | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Skin ulcer<br>subjects affected / exposed<br>occurrences (all)             | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Skin ulcer haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Swelling face<br>subjects affected / exposed<br>occurrences (all)          | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Renal and urinary disorders  |                     |                      |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)             | 3 / 35 (8.57%)<br>4 | 2 / 127 (1.57%)<br>2 |  |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)            | 1 / 35 (2.86%)<br>1 | 2 / 127 (1.57%)<br>2 |  |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)    | 0 / 35 (0.00%)<br>0 | 2 / 127 (1.57%)<br>2 |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                | 0 / 35 (0.00%)<br>0 | 2 / 127 (1.57%)<br>2 |  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)            | 1 / 35 (2.86%)<br>1 | 1 / 127 (0.79%)<br>2 |  |
| Anuria<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 35 (2.86%)<br>1 | 0 / 127 (0.00%)<br>0 |  |
| Bladder discomfort<br>subjects affected / exposed<br>occurrences (all)     | 0 / 35 (0.00%)<br>0 | 1 / 127 (0.79%)<br>1 |  |
| Bladder spasm  |                     |                      |  |

|                             |                 |                   |  |
|-----------------------------|-----------------|-------------------|--|
| subjects affected / exposed | 1 / 35 (2.86%)  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1               | 0                 |  |
| Chronic kidney disease      |                 |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Hydronephrosis              |                 |                   |  |
| subjects affected / exposed | 1 / 35 (2.86%)  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1               | 0                 |  |
| Leukocyturia                |                 |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Micturition urgency         |                 |                   |  |
| subjects affected / exposed | 1 / 35 (2.86%)  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1               | 0                 |  |
| Nephrolithiasis             |                 |                   |  |
| subjects affected / exposed | 1 / 35 (2.86%)  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1               | 0                 |  |
| Nocturia                    |                 |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Oliguria                    |                 |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Polyuria                    |                 |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Urinary retention           |                 |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Urine odour abnormal        |                 |                   |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0               | 1                 |  |
| Endocrine disorders         |                 |                   |  |
| Hypothyroidism              |                 |                   |  |
| subjects affected / exposed | 4 / 35 (11.43%) | 15 / 127 (11.81%) |  |
| occurrences (all)           | 4               | 16                |  |

|  |                       |                         |  |
|--|-----------------------|-------------------------|--|
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)            | 2 / 35 (5.71%)<br>2   | 12 / 127 (9.45%)<br>12  |  |
| Adrenal insufficiency<br>subjects affected / exposed<br>occurrences (all)      | 0 / 35 (0.00%)<br>0   | 1 / 127 (0.79%)<br>1    |  |
| Androgen deficiency<br>subjects affected / exposed<br>occurrences (all)        | 0 / 35 (0.00%)<br>0   | 1 / 127 (0.79%)<br>1    |  |
| Thyroiditis acute<br>subjects affected / exposed<br>occurrences (all)          | 0 / 35 (0.00%)<br>0   | 1 / 127 (0.79%)<br>1    |  |
| Musculoskeletal and connective tissue disorders                                |                       |                         |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 5 / 35 (14.29%)<br>15 | 28 / 127 (22.05%)<br>30 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 35 (8.57%)<br>3   | 13 / 127 (10.24%)<br>15 |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)       | 6 / 35 (17.14%)<br>7  | 7 / 127 (5.51%)<br>7    |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 35 (11.43%)<br>4  | 6 / 127 (4.72%)<br>8    |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)          | 1 / 35 (2.86%)<br>1   | 9 / 127 (7.09%)<br>10   |  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)          | 1 / 35 (2.86%)<br>1   | 8 / 127 (6.30%)<br>9    |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 35 (2.86%)<br>1   | 5 / 127 (3.94%)<br>5    |  |
| Neck pain  |                       |                         |  |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 1 / 35 (2.86%) | 4 / 127 (3.15%) |
| occurrences (all)           | 1              | 8               |
| Flank pain                  |                |                 |
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 127 (0.79%) |
| occurrences (all)           | 3              | 1               |
| Arthritis                   |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)           | 0              | 3               |
| Joint effusion              |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)           | 0              | 7               |
| Joint swelling              |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)           | 0              | 2               |
| Muscle spasms               |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)           | 1              | 1               |
| Bone pain                   |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Groin pain                  |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 1              | 0               |
| Joint instability           |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 1              | 0               |
| Muscle contracture          |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Musculoskeletal disorder    |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Myalgia intercostal         |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Myopathy                    |                |                 |

|                             |                 |                  |  |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0               | 1                |  |
| Osteoporosis                |                 |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0               | 1                |  |
| Plantar fasciitis           |                 |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)  | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 1               | 0                |  |
| Rotator cuff syndrome       |                 |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)  | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 1               | 0                |  |
| Tendon pain                 |                 |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0               | 1                |  |
| Infections and infestations |                 |                  |  |
| Urinary tract infection     |                 |                  |  |
| subjects affected / exposed | 5 / 35 (14.29%) | 10 / 127 (7.87%) |  |
| occurrences (all)           | 6               | 10               |  |
| Rash pustular               |                 |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)  | 6 / 127 (4.72%)  |  |
| occurrences (all)           | 1               | 9                |  |
| Pneumonia                   |                 |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 5 / 127 (3.94%)  |  |
| occurrences (all)           | 0               | 5                |  |
| Sinusitis                   |                 |                  |  |
| subjects affected / exposed | 2 / 35 (5.71%)  | 3 / 127 (2.36%)  |  |
| occurrences (all)           | 2               | 3                |  |
| Candida infection           |                 |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)  | 3 / 127 (2.36%)  |  |
| occurrences (all)           | 1               | 4                |  |
| Influenza                   |                 |                  |  |
| subjects affected / exposed | 1 / 35 (2.86%)  | 3 / 127 (2.36%)  |  |
| occurrences (all)           | 1               | 5                |  |
| Lung infection              |                 |                  |  |
| subjects affected / exposed | 0 / 35 (0.00%)  | 4 / 127 (3.15%)  |  |
| occurrences (all)           | 0               | 6                |  |

|                                   |                |                 |
|-----------------------------------|----------------|-----------------|
| Respiratory tract infection       |                |                 |
| subjects affected / exposed       | 0 / 35 (0.00%) | 4 / 127 (3.15%) |
| occurrences (all)                 | 0              | 4               |
| Upper respiratory tract infection |                |                 |
| subjects affected / exposed       | 2 / 35 (5.71%) | 2 / 127 (1.57%) |
| occurrences (all)                 | 2              | 2               |
| Corona virus infection            |                |                 |
| subjects affected / exposed       | 0 / 35 (0.00%) | 3 / 127 (2.36%) |
| occurrences (all)                 | 0              | 3               |
| Oral candidiasis                  |                |                 |
| subjects affected / exposed       | 2 / 35 (5.71%) | 1 / 127 (0.79%) |
| occurrences (all)                 | 3              | 2               |
| Herpes zoster                     |                |                 |
| subjects affected / exposed       | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                 | 0              | 2               |
| Pharyngitis                       |                |                 |
| subjects affected / exposed       | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                 | 0              | 3               |
| Rhinitis                          |                |                 |
| subjects affected / exposed       | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)                 | 0              | 2               |
| Tooth infection                   |                |                 |
| subjects affected / exposed       | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)                 | 1              | 1               |
| Bronchitis                        |                |                 |
| subjects affected / exposed       | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                 | 0              | 1               |
| Clostridium difficile colitis     |                |                 |
| subjects affected / exposed       | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                 | 0              | 1               |
| Clostridium difficile infection   |                |                 |
| subjects affected / exposed       | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)                 | 1              | 0               |
| Conjunctivitis                    |                |                 |
| subjects affected / exposed       | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)                 | 0              | 2               |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| Cystitis                    |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 2              | 0               |
| Device related infection    |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Diverticulitis              |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 1              | 0               |
| Gingivitis                  |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Groin infection             |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 1              | 0               |
| Hordeolum                   |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Mucosal infection           |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Oesophageal candidiasis     |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Oropharyngeal candidiasis   |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Otitis media                |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Peripheral nerve infection  |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 127 (0.00%) |
| occurrences (all)           | 1              | 0               |
| Pneumonia klebsiella        |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |

|   |                        |                         |  |
|---|------------------------|-------------------------|--|
| Pneumonia staphylococcal<br>subjects affected / exposed<br>occurrences (all)                | 0 / 35 (0.00%)<br>0    | 1 / 127 (0.79%)<br>1    |  |
| Sepsis<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 35 (0.00%)<br>0    | 1 / 127 (0.79%)<br>1    |  |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 35 (0.00%)<br>0    | 1 / 127 (0.79%)<br>1    |  |
| Vaginal infection<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 35 (0.00%)<br>0    | 1 / 127 (0.79%)<br>1    |  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 35 (0.00%)<br>0    | 1 / 127 (0.79%)<br>1    |  |
| Metabolism and nutrition disorders  |                        |                         |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 13 / 35 (37.14%)<br>13 | 25 / 127 (19.69%)<br>29 |  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 35 (8.57%)<br>3    | 16 / 127 (12.60%)<br>20 |  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 35 (5.71%)<br>2    | 12 / 127 (9.45%)<br>15  |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 35 (2.86%)<br>1    | 12 / 127 (9.45%)<br>13  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)                           | 6 / 35 (17.14%)<br>7   | 6 / 127 (4.72%)<br>7    |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 35 (5.71%)<br>2    | 6 / 127 (4.72%)<br>7    |  |
| Hypophosphataemia   |                        |                         |  |



|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 2 / 35 (5.71%) | 4 / 127 (3.15%) |
| occurrences (all)           | 2              | 4               |
| Hypercalcaemia              |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 4 / 127 (3.15%) |
| occurrences (all)           | 1              | 5               |
| Hyperglycaemia              |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 3 / 127 (2.36%) |
| occurrences (all)           | 0              | 6               |
| Hyperkalaemia               |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 3 / 127 (2.36%) |
| occurrences (all)           | 0              | 3               |
| Hyperuricaemia              |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)           | 1              | 1               |
| Hypoalbuminaemia            |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 127 (1.57%) |
| occurrences (all)           | 0              | 2               |
| Hypovolaemia                |                |                 |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 127 (0.79%) |
| occurrences (all)           | 1              | 1               |
| Cachexia                    |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Folate deficiency           |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Hypertriglyceridaemia       |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Hypervolaemia               |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Hypoglycaemia               |                |                 |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all)           | 0              | 1               |
| Insulin resistance          |                |                 |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0              | 1               |  |
| Malnutrition                |                |                 |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0              | 1               |  |
| Vitamin D deficiency        |                |                 |  |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0              | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 30 March 2017 | <p>Modified timing of safety observations in Cycle 1 to include additional monitoring during Days 1-3 and to remove monitoring on Days 6-11 to reduce the number of overall assessments and study visits; removed clinical site visits for physical examinations and ECGs for Days 4, 5, and 11 of Cycles 1 and 2.</p> <p>Added IV fluid administration on Days 1 and 2 of Cycle 1.</p> <p>Updated timing of the End of Treatment visit based on which study drug(s) the patient was receiving.</p> <p>Reduced the frequency of PK sampling in Cycle 2 from Days 1-5, 8, and 11 to Days 1 and 8 only.</p> <p>Updated inclusion criterion 8h to include an upper limit on lipase and amylase levels to <math>&lt; 3 \times \text{ULN}</math> (if there were neither clinical nor radiographic signs of pancreatitis).</p> <p>Modified the eligibility criteria to exclude patients who have a diagnosis of NSCLC and require supplemental oxygen.</p> <p>Modified the eligibility criteria to exclude patients in whom checkpoint inhibitor therapy was intolerable and required discontinuation of treatment.</p> <p>Modified and clarified the language for long-term follow up to evaluate tumor data and/or scans for patients who started a new anti-cancer therapy.</p> <p>Added a requirement that patients be re-consented if the treating physician recommends continuing treatment following disease progression.</p> <p>Added "any Grade 4 nausea or vomiting" to DLT list.</p> <p>Modified criteria for Grade 3 or 4 AEs that should not be considered a DLT</p> <p>Removed information on Grade 4 toxicities for NKTR-214 dose delay and reduction criteria</p> <p>Added information on Grade 4 amylase or lipase to the permanent treatment discontinuation criteria</p> <p>Added language "suspected" or "known" disease progression for tumor biopsies.</p> <p>Added section on IMAE reporting.</p> <p>Removed section on response criteria using irRECIST.</p> <p>Updated language in section on Changes to the Protocol to allow an administrative letter describing protocol changes to be used by the Sponsor.</p> <p>Updated section on language on quality control and quality assurance</p> |

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| 21 September 2017 | <p>Added select on-label indications for pembrolizumab (locally advanced or metastatic melanoma, locally advanced or metastatic urothelial bladder cancer, or metastatic NSCLC) as a second combination treatment option; title updated to reflect the addition of pembrolizumab.</p> <p>Added disease-specific inclusion criteria.</p> <p>Changed planned number of study sites, anticipated enrollment, and duration for infusion of NKTR-214 from 15 (<math>\pm</math>5) min to 30 (<math>\pm</math>5) min.</p> <p>Updated protocol introduction to include safety information about clinical experience with NKTR-214, and to remove nonclinical data.</p> <p>Changed inclusion criterion for demonstration of adequate organ function to within 28 days of treatment initiation and descriptions of eligibility criteria regarding duration of post-study contraception use and duration of follow up for pregnancy from 3 mos to 5.</p> <p>Modified enrollment into cohorts to clarify that each cohort may enroll any combination of patients with any of the eligible tumor types; modified to clarify that the first 3 patients in each cohort were to be dosed to allow evaluation of DLTs and that the cohort may then be immediately expanded to 6 patients if no DLT occurred in the first 3 patients.</p> <p>Changed timing for predose blood sample collection for clinical lab tests.</p> <p>Updated postdose monitoring, intensive vital sign measurements, and hydration guidelines</p> <p>Revised EOT visit, and follow-up visit time windows.</p> <p>Modified reasons for EOT.</p> <p>Clarified timing of PK assessments.</p> <p>Updated recommendations regarding treatment of infusion reactions to include NKTR-214 and pembrolizumab.</p> <p>Updated the list of AEs that should not be considered a DLT.</p> <p>Removed 24-hr reporting requirement for Gr 3 or higher imAEs.</p> <p>Specified that ECGs should be conducted predose.</p> <p>Updated timing for confirmation radiologic exam.</p> <p>Removed the requirement for HLA typing at screening.</p> <p>Removed exp. obj. to evaluate preliminary efficacy of NKTR-214 in combo with pembro and atezo</p> |
| 21 November 2017  | <p>Simplified study title.</p> <p>Lowered the minimum requirement for GFR in inclusion criterion 8e from <math>\geq 40</math> to <math>\geq 15</math> mL/min for patients with urothelial carcinoma who were cisplatin-ineligible.</p> <p>Clarified inclusion criterion 18b about known EGFR or ALK mutations applies only to non-squamous NSCLC.</p> <p>Replaced stress ECHO at baseline and at EOT with a standard ECHO; added language to allow for stress ECHO in the event of an abnormal standard ECHO, per clinical judgement; added language allowing for the flexibility to eliminate the need for a standard ECHO if deemed unnecessary by the Safety Review Committee.</p> <p>Capped continuation of treatment in patients with a confirmed complete response at a maximum of 2 years.</p> <p>Edited language about the end of treatment visit to clarify timing</p> <p>Corrected inconsistent language in the radiographic tumor assessment section and long-term follow-up section.</p> <p>Changed timing for the required on-treatment tumor biopsy from Days 15-25 to Days 15-21 after the first dose.</p> <p>Changed duration of stable disease from <math>\geq 84</math> days (12 weeks) to <math>\geq 7</math> weeks for the definition clinical benefit rate.</p> <p>Added collection of bi-dimensional measurements from sites.</p> <p>Added language allowing prophylaxis for flu-like symptoms and/or rash/pruritus</p>   |
| 29 May 2018       | <p>Removed dose escalation cohorts; NKTR-214 dose was established at 0.006 mg/kg given IV q3w.</p> <p>Removed description of DLT.</p> <p>Modified tumor types and treatments to be studied in each tumor type.</p> <p>Updated of inclusion/exclusion criteria.</p> <p>Aligned with PIVOT-02 Amendment 6.0.</p>  |

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| 20 August 2019    | <p>Updated figure of study schematic and schedule of assessments tables.</p> <p>Added the INN for NKTR-214 to the protocol.</p> <p>Updated clinical experience with NKTR-214.</p> <p>Added dose optimization cohorts and dose expansion cohort and rationale for their addition to the protocol.</p> <p>Added description of DLT.</p> <p>Modified of the tumor types and treatments to be studied in each tumor type.</p> <p>Updated inclusion/exclusion criteria</p> <p>Aligned with PIVOT-02 Amendment 6.0</p>   |
| 11 September 2019 | First version of protocol submitted to Germany   |
| 06 December 2019  | Removed possibility of collecting survival data beyond the end of study period   |
| 10 January 2020   | <p>Exclusion of patients with PD-L1 &lt; 50% from first-line NSCLC dose expansion cohorts</p> <p>Addition of ROS1 among tumor aberrations excluded in first line NSCLC dose expansion population cohorts</p> <p>Changed inclusion limit for patients from systolic &lt; 150 mm Hg to &lt; 140 mm Hg</p> <p>Added requirement of social security coverage</p> <p>Added exclusions of patients who received a live vaccine within 30 days of first study dose and patients with known history of active tuberculosis</p>   |
| 10 February 2020  | <p>Updated the NKTR-214 clinical experience to include a summary of the CVA events observed in 16-214-02</p> <p>Implemented add'l safety measures to mitigate the risk of CVA events</p> <p>Added plasma samples for exploratory biomarker analyses for CVA characterization</p> <p>Modified instructions for NKTR-214 dose delay/reduction and criteria to resume study drug</p> <p>Added the re-trtmt criteria for renal fx and permanent trtmt discon in the CVA AE mngmt algorithm, the local lab tests prior to study drug, and a new appx to clarify definitions and methods of contraception for women of childbearing potential</p> <p>Updated inclusion criteria in both the dose optimization and dose exp cohorts such that pts must not have progressed within 6 mos of receiving radiation, surgery, adj, neoadj, or systemic therapy for cancer trtmt</p> <p>Clarified the definition of a line of prior therapy</p> <p>Excluded pts with c-ros oncogene and BRAF v600e for the dose exp phase</p> <p>Changed the exclusion for cardiovascular hx from the previous 2 yrs to 12 mos</p> <p>Excluded pts in subgroup PD-L1 &lt; 1-49%, updated screening blood pressure to systolic &lt; 140 mm Hg, added requirement that enrolled pts be affiliated to a Social Security System; and excluded pts who received a live vaccine within 30d prior to first dose and those with a known history of active tuberculosis (France only)</p> <p>Added that pelvic radiographic assessment is NA (Germany only)</p> <p>Updated NKTR-214 MOA, SOE, hydration guidelines, SAE reporting rqmts to indicate that AEs of special interest followed the same timeline as SAE reporting, and the recommendation for the contraception timeperiod for men following the last dose to 4 mos</p> <p>Removed possibility of collecting survival data beyond the end of study</p> <p>Added a section on the effect of NKTR-214 on conmed metabolism and the CVA AE mngmt algorithm, an appx on CVA mngmt algorithm, and sections on imAEs and potential DILI and section on AEs of special interest to cover CVA events</p> <p>Divided Appx 1 displaying lab tests</p> |
| 01 November 2020  | Added specific guidance in the event of cytokine release syndrome occurrence   |

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| 23 December 2020 | <p>Added Cohort 3 as contingency plan if Cohort 2 fails; 58 response evaluable first-line NSCLC patients could be enrolled in Cohort 3.</p> <p>Added cohorts of a chemotherapy combination to support Phase 3 with NKTR-214/pembrolizumab chemotherapy combination: Cohort 4 (non-squamous) and Cohort 5 (squamous).</p> <p>Added CRS appendix.</p> <p>Updated with newest version of CTCAE (per CTCAE v5.0).</p> <p>Updated the language regarding minimum duration on study for stable disease.</p> <p>Updated text on regarding flushing of the IV line after NKTR-214 infusion</p> <p>Updated with administrative clarifications and edits</p> |
| 27 April 2021    | <p>Added early stopping and safety monitoring rules for dose expansion Cohorts 4 and 5.</p> <p>Added DLTs to be evaluated in expansion phases.</p>   |

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

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| This study was terminated early due to closure of the NKTR-214 clinical program. |
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