



## Clinical trial results:

**A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2018-002180-25   |
| Trial protocol           | BE GB FR IT      |
| Global end of trial date | 18 November 2024 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 18 March 2026 |
| First version publication date | 18 March 2026 |

### Trial information

#### Trial identification

|                       |                      |
|-----------------------|----------------------|
| Sponsor protocol code | ETOP 13-18 BEAT-meso |
|-----------------------|----------------------|

#### Additional study identifiers

|                                    |                       |
|------------------------------------|-----------------------|
| ISRCTN number                      | -                     |
| ClinicalTrials.gov id (NCT number) | NCT03762018           |
| WHO universal trial number (UTN)   | -                     |
| Other trial identifiers            | Roche Number: MO40388 |

Notes:

#### Sponsors

|                              |                                                                                                                        |
|------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | ETOP IBCSG Partners Foundation                                                                                         |
| Sponsor organisation address | Effingerstrasse 33, Bern, Switzerland, 3008                                                                            |
| Public contact               | ETOP IBCSG Partners Coordinating Center, ETOP IBCSG Partners Foundation, +41 315119400, etop-regulatory@etop.ibcsg.org |
| Scientific contact           | ETOP IBCSG Partners Coordinating Center, ETOP IBCSG Partners Foundation, +41 315119400, etop-regulatory@etop.ibcsg.org |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 25 November 2024  |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 01 September 2023 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 18 November 2024  |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this trial is to assess the effect of atezolizumab in terms of PFS and OS when added to standard of care (carboplatin/pemetrexed/bevacizumab), as first-line treatment of advanced MPM.

Protection of trial subjects:

Participating institutions' ethics committees or Institutional Review Boards approved the trial according to local laws and regulations. All patients gave written informed consent, and the trial was performed in compliance with the Helsinki Declaration. The Data Safety and Monitoring Board reviewed the data from this research throughout the study.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 30 April 2019 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Switzerland: 66     |
| Country: Number of subjects enrolled | Spain: 84           |
| Country: Number of subjects enrolled | United Kingdom: 139 |
| Country: Number of subjects enrolled | Belgium: 22         |
| Country: Number of subjects enrolled | France: 21          |
| Country: Number of subjects enrolled | Italy: 68           |
| Worldwide total number of subjects   | 400                 |
| EEA total number of subjects         | 195                 |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |

|                           |     |
|---------------------------|-----|
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 102 |
| From 65 to 84 years       | 292 |
| 85 years and over         | 6   |

## Subject disposition

### Recruitment

Recruitment details:

Overall, 400 patients were randomized from April 30, 2019 to March 07, 2022 (randomization date of the last patient). Randomized patients come from 38 centers in 6 European countries (10 in United Kingdom, 9 in Switzerland, 7 in Spain, 6 in Italy, 4 in France, 2 in Belgium).

### Pre-assignment

Screening details:

46 patients were not randomized in the trial, indicated as screening failures.

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | ABC Arm |

Arm description:

4-6 cycles chemotherapy: Carboplatin AUC 5 + pemetrexed 500 mg/m<sup>2</sup>, D1Q3W plus  
Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity plus  
Atezolizumab 1200 mg D1Q3W until PD, refusal or unacceptable toxicity

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Atezolizumab                          |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

1200 mg D1Q3W until PD, refusal or unacceptable toxicity

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Investigational medicinal product name | Bevacizumab                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

15mg/kg D1Q3W until PD, refusal or unacceptable toxicity

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

Dosage and administration details:

4-6 cycles chemotherapy: Carboplatin AUC 5, D1Q3W

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

Dosage and administration details:

4-6 cycles chemotherapy: pemetrexed 500 mg/m<sup>2</sup>, D1Q3W

|                  |        |
|------------------|--------|
| <b>Arm title</b> | BC Arm |
|------------------|--------|

Arm description:

4-6 cycles chemotherapy: Carboplatin AUC 5 + pemetrexed 500 mg/m<sup>2</sup>, D1Q3W plus

Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | Bevacizumab                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

15mg/kg D1Q3W until PD, refusal or unacceptable toxicity

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

Dosage and administration details:

4-6 cycles chemotherapy: Carboplatin AUC 5, D1Q3W

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

Dosage and administration details:

4-6 cycles chemotherapy: pemetrexed 500 mg/m<sup>2</sup>, D1Q3W

| <b>Number of subjects in period 1</b> | ABC Arm | BC Arm |
|---------------------------------------|---------|--------|
| Started                               | 200     | 200    |
| Completed                             | 51      | 48     |
| Not completed                         | 149     | 152    |
| Death                                 | 145     | 150    |
| Withdrawal/Lost to follow-up          | 4       | 2      |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                     |         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                                                                                                                                                                               | ABC Arm |
| Reporting group description:<br>4-6 cycles chemotherapy: Carboplatin AUC 5 + pemetrexed 500 mg/m2, D1Q3W plus<br>Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity plus<br>Atezolizumab 1200 mg D1Q3W until PD, refusal or unacceptable toxicity |         |
| Reporting group title                                                                                                                                                                                                                                               | BC Arm  |
| Reporting group description:<br>4-6 cycles chemotherapy: Carboplatin AUC 5 + pemetrexed 500 mg/m2, D1Q3W plus<br>Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity                                                                               |         |

| Reporting group values                                                                                                                                                                                            | ABC Arm      | BC Arm       | Total |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------|-------|
| Number of subjects                                                                                                                                                                                                | 200          | 200          | 400   |
| Age categorical<br>Units: Subjects                                                                                                                                                                                |              |              |       |
| In utero                                                                                                                                                                                                          |              |              | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks)                                                                                                                                                             |              |              | 0     |
| Newborns (0-27 days)                                                                                                                                                                                              |              |              | 0     |
| Infants and toddlers (28 days-23<br>months)                                                                                                                                                                       |              |              | 0     |
| Children (2-11 years)                                                                                                                                                                                             |              |              | 0     |
| Adolescents (12-17 years)                                                                                                                                                                                         |              |              | 0     |
| Adults (18-64 years)                                                                                                                                                                                              |              |              | 0     |
| From 65-84 years                                                                                                                                                                                                  |              |              | 0     |
| 85 years and over                                                                                                                                                                                                 |              |              | 0     |
| Age continuous<br>Units: years                                                                                                                                                                                    |              |              |       |
| median                                                                                                                                                                                                            | 70.7         | 70.1         |       |
| full range (min-max)                                                                                                                                                                                              | 42.3 to 87.6 | 47.7 to 88.2 | -     |
| Gender categorical<br>Units: Subjects                                                                                                                                                                             |              |              |       |
| Female                                                                                                                                                                                                            | 40           | 44           | 84    |
| Male                                                                                                                                                                                                              | 160          | 156          | 316   |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                     |              |              |       |
| White                                                                                                                                                                                                             | 199          | 200          | 399   |
| Black                                                                                                                                                                                                             | 1            | 0            | 1     |
| Smoking status                                                                                                                                                                                                    |              |              |       |
| Current smoker: Still smokes cigarettes, Former smoker: Smoked at least 100 cigarettes in the past<br>during the whole life, Never smoker: Smoked 0-99 cigarettes during the whole life.                          |              |              |       |
| Units: Subjects                                                                                                                                                                                                   |              |              |       |
| Current smoker                                                                                                                                                                                                    | 15           | 11           | 26    |
| Former smoker                                                                                                                                                                                                     | 99           | 99           | 198   |
| Never smoked                                                                                                                                                                                                      | 86           | 90           | 176   |
| ECOG Performance Status                                                                                                                                                                                           |              |              |       |
| 0: Fully active, able to carry on all pre-disease performance without restriction; 1: Restricted in<br>physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e. |              |              |       |

|                                                                                                                                                                                                                                                                                       |     |     |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|-----|
| g., light house work, office work.                                                                                                                                                                                                                                                    |     |     |     |
| Units: Subjects                                                                                                                                                                                                                                                                       |     |     |     |
| Status 0                                                                                                                                                                                                                                                                              | 80  | 61  | 141 |
| Status 1                                                                                                                                                                                                                                                                              | 119 | 139 | 258 |
| Unknown/Missing                                                                                                                                                                                                                                                                       | 1   | 0   | 1   |
| Stage                                                                                                                                                                                                                                                                                 |     |     |     |
| Stage is based on the 8th TNM classification for Malignant Pleural Mesothelioma (American Joint Committee on Cancer).                                                                                                                                                                 |     |     |     |
| Units: Subjects                                                                                                                                                                                                                                                                       |     |     |     |
| IV                                                                                                                                                                                                                                                                                    | 43  | 41  | 84  |
| Other                                                                                                                                                                                                                                                                                 | 157 | 159 | 316 |
| Histology                                                                                                                                                                                                                                                                             |     |     |     |
| Units: Subjects                                                                                                                                                                                                                                                                       |     |     |     |
| Epitheloid                                                                                                                                                                                                                                                                            | 157 | 154 | 311 |
| Non pure epitheloid                                                                                                                                                                                                                                                                   | 43  | 46  | 89  |
| Asbestos exposure                                                                                                                                                                                                                                                                     |     |     |     |
| Units: Subjects                                                                                                                                                                                                                                                                       |     |     |     |
| Yes                                                                                                                                                                                                                                                                                   | 84  | 89  | 173 |
| Possible                                                                                                                                                                                                                                                                              | 51  | 58  | 109 |
| No                                                                                                                                                                                                                                                                                    | 48  | 33  | 81  |
| Unknown/Missing                                                                                                                                                                                                                                                                       | 17  | 20  | 37  |
| PD-L1 TPS%                                                                                                                                                                                                                                                                            |     |     |     |
| Units: Subjects                                                                                                                                                                                                                                                                       |     |     |     |
| <1                                                                                                                                                                                                                                                                                    | 117 | 98  | 215 |
| 1-49                                                                                                                                                                                                                                                                                  | 56  | 66  | 122 |
| ≥50                                                                                                                                                                                                                                                                                   | 21  | 26  | 47  |
| Unknown/Missing                                                                                                                                                                                                                                                                       | 6   | 10  | 16  |
| EORTC prognostic score                                                                                                                                                                                                                                                                |     |     |     |
| EORTC PROGNOSTIC SCORE: Curran et al. Journal of Clinical Oncology. 1998 Jan; Vol16:145-152                                                                                                                                                                                           |     |     |     |
| Units: Subjects                                                                                                                                                                                                                                                                       |     |     |     |
| Good prognosis                                                                                                                                                                                                                                                                        | 146 | 134 | 280 |
| Poor prognosis                                                                                                                                                                                                                                                                        | 54  | 66  | 120 |
| Mesothelioma risk score (MRS)                                                                                                                                                                                                                                                         |     |     |     |
| Mesothelioma risk score (MRS): Banna et al. Lung Cancer. 2022 Jul; 169:77-83<br>The risk factors are baseline systemic immune-inflammatory index (good: < 1,250 vs poor: ≥ 1,250) and baseline haemoglobin (good: ≥ LLN vs poor: < LLN) (LLN = 135 for males, LLN = 120 for females)) |     |     |     |
| Units: Subjects                                                                                                                                                                                                                                                                       |     |     |     |
| 0-Favorable                                                                                                                                                                                                                                                                           | 72  | 64  | 136 |
| 1-Intermediate                                                                                                                                                                                                                                                                        | 66  | 63  | 129 |
| 2-Poor                                                                                                                                                                                                                                                                                | 62  | 73  | 135 |
| Medical history                                                                                                                                                                                                                                                                       |     |     |     |
| Units: Subjects                                                                                                                                                                                                                                                                       |     |     |     |
| Yes                                                                                                                                                                                                                                                                                   | 189 | 187 | 376 |
| No                                                                                                                                                                                                                                                                                    | 11  | 13  | 24  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                     |         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                                                                                                                                                                               | ABC Arm |
| Reporting group description:<br>4-6 cycles chemotherapy: Carboplatin AUC 5 + pemetrexed 500 mg/m2, D1Q3W plus<br>Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity plus<br>Atezolizumab 1200 mg D1Q3W until PD, refusal or unacceptable toxicity |         |
| Reporting group title                                                                                                                                                                                                                                               | BC Arm  |
| Reporting group description:<br>4-6 cycles chemotherapy: Carboplatin AUC 5 + pemetrexed 500 mg/m2, D1Q3W plus<br>Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity                                                                               |         |

### Primary: Overall Survival (OS)

|                                                                                                                                                                                                                                                                                                                                                                                                |                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                | Overall Survival (OS) |
| End point description:<br>Overall survival is defined as the time from the date of randomisation until death from any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients without post-baseline information will be censored at the date of randomization (plus 1 day). |                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                 | Primary               |
| End point timeframe:<br>Evaluated up to approximately 58 months from the randomisation of the first patient.                                                                                                                                                                                                                                                                                   |                       |

| End point values                 | ABC Arm             | BC Arm              |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 200 <sup>[1]</sup>  | 200 <sup>[2]</sup>  |  |  |
| Units: month                     |                     |                     |  |  |
| median (confidence interval 95%) | 20.5 (17.5 to 23.3) | 18.1 (15.7 to 20.9) |  |  |

Notes:

[1] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

[2] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Statistical Analysis 1 |
| Statistical analysis description:<br>The study was designed to test the hypothesis that addition of Atezolizumab to Bevacizumab and chemotherapy leads to an increase in median OS from 17 months with Bevacizumab and chemotherapy alone to 24 months. According to the study design, this corresponds to a HR of 0.708. Using the log-rank test stratified by the randomization stratification factors (histological subtype and stage), 284 deaths were required to achieve the trial goal with 82.1% power at a 1-sided significance level of 2.5%. |                        |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | BC Arm v ABC Arm       |

|                                         |                       |
|-----------------------------------------|-----------------------|
| Number of subjects included in analysis | 400                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.14 <sup>[3]</sup> |
| Method                                  | Regression, Cox       |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 0.84                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.66                  |
| upper limit                             | 1.06                  |

Notes:

[3] - 1-sided significance level of 2.5%.

### Secondary: Progression-free Survival (PFS) according to the mRECIST v1.1

|                                                                                                                                                                                                                                                                                                                                                                                            |                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                            | Progression-free Survival (PFS) according to the mRECIST v1.1 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                     |                                                               |
| PFS is defined as the time from the date of randomisation until documented progression (according to the mRECIST v1.1) or death, if progression is not documented. Censoring (for participants without a PFS/death event) will occur at the date of last tumour assessment. Patients without a post-baseline tumour assessment will be censored at the date of randomization (plus 1 day). |                                                               |
| End point type                                                                                                                                                                                                                                                                                                                                                                             | Secondary                                                     |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                       |                                                               |
| Evaluated up to approximately 58 months from the randomisation of the first patient.                                                                                                                                                                                                                                                                                                       |                                                               |

| End point values                 | ABC Arm            | BC Arm             |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 200 <sup>[4]</sup> | 200 <sup>[5]</sup> |  |  |
| Units: Month                     |                    |                    |  |  |
| median (confidence interval 95%) | 9.2 (8.1 to 10.9)  | 7.6 (6.9 to 8.3)   |  |  |

Notes:

[4] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

[5] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR)

|                                                                                                                                                                                                                                                                                                                                     |                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                     | Objective Response Rate (ORR) |
| End point description:                                                                                                                                                                                                                                                                                                              |                               |
| Objective Response Rate (ORR) is defined as the percentage of patients that achieve a best overall response [complete response (CR) or partial response (PR)] evaluated according to the mRECIST v1.1 across all post-randomization time-points until the end of protocol treatment. Confirmation of response will not be required. |                               |
| End point type                                                                                                                                                                                                                                                                                                                      | Secondary                     |
| End point timeframe:                                                                                                                                                                                                                                                                                                                |                               |
| Evaluated up to approximately 58 months from the randomisation of the first patient.                                                                                                                                                                                                                                                |                               |

| End point values            | ABC Arm            | BC Arm             |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 200 <sup>[6]</sup> | 200 <sup>[7]</sup> |  |  |
| Units: Participant          | 110                | 98                 |  |  |

Notes:

[6] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

[7] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control (DC) at 24 weeks

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Disease Control (DC) at 24 weeks |
|-----------------|----------------------------------|

End point description:

Disease Control (DC) is defined as complete or partial response, or disease stabilisation at 24 weeks (+/- 10 days). Patients with no available scan at this time period, but with scan performed before 24 weeks - 10 days and scan performed after 24 weeks + 10 days showing disease control, will be considered as disease control.

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

End point timeframe:

Evaluated up to approximately 58 months from the randomisation of the first patient.

| End point values            | ABC Arm            | BC Arm             |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 200 <sup>[8]</sup> | 200 <sup>[9]</sup> |  |  |
| Units: Participant          | 134                | 115                |  |  |

Notes:

[8] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

[9] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Treatment Failure (TTF)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Time to Treatment Failure (TTF) |
|-----------------|---------------------------------|

End point description:

Time to Treatment Failure (TTF) is defined as the time from the date of randomisation to discontinuation of protocol treatment for any reason (including progression of disease, death, discontinuation of at least one of the drugs consisting the treatment combination due to any reason, such as toxicity or refusal). Censoring will occur at the last follow-up date.

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

End point timeframe:

Evaluated up to approximately 58 months from the randomisation of the first patient.

| End point values                 | ABC Arm             | BC Arm              |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 200 <sup>[10]</sup> | 200 <sup>[11]</sup> |  |  |
| Units: month                     |                     |                     |  |  |
| median (confidence interval 95%) | 6.5 (5.6 to 7.4)    | 6.5 (5.7 to 7.0)    |  |  |

Notes:

[10] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

[11] - Efficacy population (Intention-To-Treat cohort of all randomised patients)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DoR)

|                 |                            |
|-----------------|----------------------------|
| End point title | Duration of Response (DoR) |
|-----------------|----------------------------|

End point description:

Duration of Response (DoR) is defined as the interval from the date of first documentation of objective response (complete response or partial response, according to the mRECIST v1.1) to the date of first documented progression/relapse or death.

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

End point timeframe:

Evaluated up to approximately 58 months from the randomisation of the first patient.

| End point values                 | ABC Arm             | BC Arm             |  |  |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type               | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed      | 110 <sup>[12]</sup> | 98 <sup>[13]</sup> |  |  |
| Units: Month                     |                     |                    |  |  |
| median (confidence interval 95%) | 8.2 (6.8 to 9.7)    | 5.6 (4.8 to 7.0)   |  |  |

Notes:

[12] - Patients with objective response

[13] - Patients with objective response

## Statistical analyses

No statistical analyses for this end point

## Secondary: Quality of Life (QoL)

|                 |                       |
|-----------------|-----------------------|
| End point title | Quality of Life (QoL) |
|-----------------|-----------------------|

End point description:

QoL will be assessed by the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso) an 8-item questionnaire including five symptoms (i.e., appetite loss, fatigue, cough, dyspnoea, and pain) and three items addressing symptomatic distress, normal activity, and global QoL. The primary QoL endpoint will be the change in the LCSS total score (average of all 8 items) from baseline to 12 weeks after treatment start.

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

End point timeframe:

Evaluated up to approximately 58 months from the randomisation of the first patient.

| End point values                              | ABC Arm             | BC Arm              |  |  |
|-----------------------------------------------|---------------------|---------------------|--|--|
| Subject group type                            | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                   | 157 <sup>[14]</sup> | 155 <sup>[15]</sup> |  |  |
| Units: Change in the LCSS average total score |                     |                     |  |  |
| median (confidence interval 95%)              | 0.4 (-2.3 to 3.0)   | 2.1 (-0.4 to 4.7)   |  |  |

Notes:

[14] - rando pts who had baseline assessment & at least 1 on-treatment post-baseline score for any LCSS-Meso item

[15] - rando pts who had baseline assessment & at least 1 on-treatment post-baseline score for any LCSS-Meso item

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adverse Events

|                 |                |
|-----------------|----------------|
| End point title | Adverse Events |
|-----------------|----------------|

End point description:

Adverse events, according to CTCAE v5.0, will be recorded from date of signature of informed consent until 90 days after the last dose of protocol treatment.

#### Analysis Population Description

Safety population (all patients who received at least 1 dose of trial treatment). There is one patient assigned in the BC arm who actually received ABC treatment. For the safety analysis the patient is evaluated according to the treatment he/she received (ABC treatment), irrespective of the allocated treatment at randomization.

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

End point timeframe:

Evaluated up to approximately 58 months from the randomisation of the first patient.

| End point values            | ABC Arm         | BC Arm          |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 199             | 199             |  |  |
| Units: Participant          | 197             | 197             |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From date of signature of informed consent until 90 days after the last dose of protocol treatment

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

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 5.0 |
|--------------------|-----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | ABC Arm |
|-----------------------|---------|

Reporting group description:

There is one patient assigned in the BC arm who actually received ABC treatment.

For the safety analysis the patient is evaluated according to the treatment he/she received (ABC treatment), irrespective of the allocated treatment at randomization

|                       |        |
|-----------------------|--------|
| Reporting group title | BC Arm |
|-----------------------|--------|

Reporting group description: -

| Serious adverse events                                              | ABC Arm           | BC Arm            |  |
|---------------------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed                                         | 94 / 199 (47.24%) | 64 / 199 (32.16%) |  |
| number of deaths (all causes)                                       | 145               | 150               |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Adenocarcinoma                                                      |                   |                   |  |
| subjects affected / exposed                                         | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Chronic myeloid leukemia                                            |                   |                   |  |
| subjects affected / exposed                                         | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Prostate adenocarcinoma                                             |                   |                   |  |
| subjects affected / exposed                                         | 2 / 199 (1.01%)   | 0 / 199 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Small cell neuroendocrine carcinoma                                 |                   |                   |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Urinary bladder nodule (left trigone region)    |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Arterial thromboembolism                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hematoma                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral ischemia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Superficial thrombophlebitis                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thromboembolic event                            |                 |                 |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 5 / 199 (2.51%) | 5 / 199 (2.51%) |  |
| occurrences causally related to treatment / all      | 4 / 5           | 4 / 5           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Elective surgery popliteal aneurysm                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Death NOS                                            |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1           |  |
| Fever                                                |                 |                 |  |
| subjects affected / exposed                          | 8 / 199 (4.02%) | 4 / 199 (2.01%) |  |
| occurrences causally related to treatment / all      | 6 / 8           | 1 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Flu like symptoms                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General clinical conditions worsening                |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General status alteration                            |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Generalized edema                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Lumbar spine joint range of motion decreased    |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Allergic reaction                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 2 / 199 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Autoimmune disorder                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Bronchopulmonary hemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease (COPD)    |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cough                                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnea                                         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 6 / 199 (3.02%) | 4 / 199 (2.01%) |  |
| occurrences causally related to treatment / all | 3 / 6           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Organized pneumonia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleuric pain                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 199 (1.51%) | 2 / 199 (1.01%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusion                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Aspartate aminotransferase increased            |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutrophil count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 2 / 199 (1.01%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Injury, poisoning and procedural complications  |                 |                 |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infusion related reaction                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Asystole                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chest pain - cardiac                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Heart failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 3 / 199 (1.51%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocarditis                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |

|                                                              |                 |                 |  |
|--------------------------------------------------------------|-----------------|-----------------|--|
| Supraventricular tachycardia<br>subjects affected / exposed  | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Ventricular arrhythmia<br>subjects affected / exposed        | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                                     |                 |                 |  |
| Cognitive disturbance<br>subjects affected / exposed         | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Headache<br>subjects affected / exposed                      | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Intracranial hemorrhage<br>subjects affected / exposed       | 2 / 199 (1.01%) | 1 / 199 (0.50%) |  |
| occurrences causally related to<br>treatment / all           | 1 / 2           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 1           | 1 / 1           |  |
| Neuralgia<br>subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 1 / 2           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Seizure<br>subjects affected / exposed                       | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Syncope                                                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |  |
| <b>Anemia</b>                                   |                 |                 |  |
| subjects affected / exposed                     | 5 / 199 (2.51%) | 2 / 199 (1.01%) |  |
| occurrences causally related to treatment / all | 4 / 5           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Febrile neutropenia</b>                      |                 |                 |  |
| subjects affected / exposed                     | 6 / 199 (3.02%) | 2 / 199 (1.01%) |  |
| occurrences causally related to treatment / all | 6 / 6           | 2 / 2           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| <b>Immune thrombocytopenic purpura</b>          |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Pancytopenia</b>                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |
| <b>Abdominal pain</b>                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Anal fistula</b>                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Colitis</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 2 / 199 (1.01%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Colonic obstruction</b>                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colonic perforation                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhea                                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphagia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric hemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 2 / 199 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower gastrointestinal hemorrhage               |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Proctitis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal perforation                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Typhlitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Bullous dermatitis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (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                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin ulceration                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hematuria                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephritis                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 199 (1.51%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal biopsy                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal toxicity                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Adrenal insufficiency                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypophysitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypothyroidism                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (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 |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myositis                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bacteremia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| COVID-19 infection                              |                 |                  |  |
| subjects affected / exposed                     | 7 / 199 (3.52%) | 2 / 199 (1.01%)  |  |
| occurrences causally related to treatment / all | 1 / 7           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Device related infection                        |                 |                  |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Fungemia                                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Infection (unknown source)                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Lung infection                                  |                 |                  |  |
| subjects affected / exposed                     | 9 / 199 (4.52%) | 12 / 199 (6.03%) |  |
| occurrences causally related to treatment / all | 2 / 9           | 5 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            |  |
| Pleural infection                               |                 |                  |  |
| subjects affected / exposed                     | 3 / 199 (1.51%) | 1 / 199 (0.50%)  |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Port-a-cath infection                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Sepsis                                          |                 |                  |  |
| subjects affected / exposed                     | 8 / 199 (4.02%) | 6 / 199 (3.02%)  |  |
| occurrences causally related to treatment / all | 8 / 8           | 4 / 6            |  |
| deaths causally related to treatment / all      | 3 / 3           | 0 / 2            |  |
| Skin infection                                  |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory infection                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 2 / 199 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Anorexia                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycemia                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hypomagnesemia</b>                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hyponatremia</b>                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                                          | ABC Arm            | BC Arm             |  |
|----------------------------------------------------------------------------|--------------------|--------------------|--|
| <b>Total subjects affected by non-serious adverse events</b>               |                    |                    |  |
| subjects affected / exposed                                                | 197 / 199 (98.99%) | 197 / 199 (98.99%) |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                    |                    |  |
| <b>Cyst buttock (right)</b>                                                |                    |                    |  |
| subjects affected / exposed                                                | 0 / 199 (0.00%)    | 1 / 199 (0.50%)    |  |
| occurrences (all)                                                          | 0                  | 1                  |  |
| <b>Nasal polyp</b>                                                         |                    |                    |  |
| subjects affected / exposed                                                | 1 / 199 (0.50%)    | 0 / 199 (0.00%)    |  |
| occurrences (all)                                                          | 1                  | 0                  |  |
| <b>Tumor pain</b>                                                          |                    |                    |  |
| subjects affected / exposed                                                | 2 / 199 (1.01%)    | 8 / 199 (4.02%)    |  |
| occurrences (all)                                                          | 2                  | 8                  |  |
| <b>Vascular disorders</b>                                                  |                    |                    |  |
| <b>Arterial thromboembolism</b>                                            |                    |                    |  |
| subjects affected / exposed                                                | 1 / 199 (0.50%)    | 0 / 199 (0.00%)    |  |
| occurrences (all)                                                          | 1                  | 0                  |  |
| <b>Flushing</b>                                                            |                    |                    |  |
| subjects affected / exposed                                                | 1 / 199 (0.50%)    | 1 / 199 (0.50%)    |  |
| occurrences (all)                                                          | 1                  | 1                  |  |
| <b>Hematoma</b>                                                            |                    |                    |  |

|                                     |                   |                   |  |
|-------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed         | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 1                 | 1                 |  |
| Hot flashes                         |                   |                   |  |
| subjects affected / exposed         | 2 / 199 (1.01%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 2                 | 1                 |  |
| Hypertension                        |                   |                   |  |
| subjects affected / exposed         | 72 / 199 (36.18%) | 62 / 199 (31.16%) |  |
| occurrences (all)                   | 72                | 62                |  |
| Hypotension                         |                   |                   |  |
| subjects affected / exposed         | 5 / 199 (2.51%)   | 3 / 199 (1.51%)   |  |
| occurrences (all)                   | 5                 | 3                 |  |
| Intracranial aneurysm               |                   |                   |  |
| subjects affected / exposed         | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 0                 | 1                 |  |
| Leg capillaritis                    |                   |                   |  |
| subjects affected / exposed         | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                   | 1                 | 0                 |  |
| Lymphedema                          |                   |                   |  |
| subjects affected / exposed         | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 1                 | 1                 |  |
| Phlebitis                           |                   |                   |  |
| subjects affected / exposed         | 2 / 199 (1.01%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 2                 | 1                 |  |
| Pulmonary arteria infiltration      |                   |                   |  |
| subjects affected / exposed         | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                   | 1                 | 0                 |  |
| Superficial thrombophlebitis        |                   |                   |  |
| subjects affected / exposed         | 2 / 199 (1.01%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 2                 | 1                 |  |
| Sylvic bifurcation aneurysm (right) |                   |                   |  |
| subjects affected / exposed         | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                   | 1                 | 0                 |  |
| Thromboembolic event                |                   |                   |  |
| subjects affected / exposed         | 16 / 199 (8.04%)  | 8 / 199 (4.02%)   |  |
| occurrences (all)                   | 16                | 8                 |  |
| Surgical and medical procedures     |                   |                   |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| Cataract surgery                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 199 (0.00%) | 3 / 199 (1.51%) |  |
| occurrences (all)                                    | 0               | 3               |  |
| Central venous access device surgery                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                    | 0               | 1               |  |
| Dental surgery                                       |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                    | 1               | 0               |  |
| Drain removal                                        |                 |                 |  |
| subjects affected / exposed                          | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                    | 0               | 1               |  |
| Electrophysiology                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                    | 0               | 1               |  |
| Exophytic lingual lesion extraction                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                    | 0               | 1               |  |
| Eyelid intervention (left)                           |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                    | 1               | 0               |  |
| Pleurectomy (left radical decortication)             |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                    | 1               | 0               |  |
| Port-a-cath blockage                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                    | 1               | 1               |  |
| Tooth extraction                                     |                 |                 |  |
| subjects affected / exposed                          | 4 / 199 (2.01%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                    | 4               | 1               |  |
| Total hip replacement (left)                         |                 |                 |  |
| subjects affected / exposed                          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                    | 1               | 0               |  |
| General disorders and administration site conditions |                 |                 |  |

|                             |                    |                    |
|-----------------------------|--------------------|--------------------|
| Asthenia                    |                    |                    |
| subjects affected / exposed | 0 / 199 (0.00%)    | 1 / 199 (0.50%)    |
| occurrences (all)           | 0                  | 1                  |
| Chills                      |                    |                    |
| subjects affected / exposed | 2 / 199 (1.01%)    | 3 / 199 (1.51%)    |
| occurrences (all)           | 2                  | 3                  |
| Cold syndrome               |                    |                    |
| subjects affected / exposed | 0 / 199 (0.00%)    | 1 / 199 (0.50%)    |
| occurrences (all)           | 0                  | 1                  |
| Dysphonia                   |                    |                    |
| subjects affected / exposed | 0 / 199 (0.00%)    | 1 / 199 (0.50%)    |
| occurrences (all)           | 0                  | 1                  |
| Edema face                  |                    |                    |
| subjects affected / exposed | 0 / 199 (0.00%)    | 1 / 199 (0.50%)    |
| occurrences (all)           | 0                  | 1                  |
| Edema limbs                 |                    |                    |
| subjects affected / exposed | 21 / 199 (10.55%)  | 15 / 199 (7.54%)   |
| occurrences (all)           | 21                 | 15                 |
| Edema trunk                 |                    |                    |
| subjects affected / exposed | 1 / 199 (0.50%)    | 0 / 199 (0.00%)    |
| occurrences (all)           | 1                  | 0                  |
| Facial pain                 |                    |                    |
| subjects affected / exposed | 1 / 199 (0.50%)    | 0 / 199 (0.00%)    |
| occurrences (all)           | 1                  | 0                  |
| Fatigue                     |                    |                    |
| subjects affected / exposed | 113 / 199 (56.78%) | 110 / 199 (55.28%) |
| occurrences (all)           | 113                | 110                |
| Fever                       |                    |                    |
| subjects affected / exposed | 35 / 199 (17.59%)  | 13 / 199 (6.53%)   |
| occurrences (all)           | 35                 | 13                 |
| Flu like symptoms           |                    |                    |
| subjects affected / exposed | 9 / 199 (4.52%)    | 8 / 199 (4.02%)    |
| occurrences (all)           | 9                  | 8                  |
| Gait disturbance            |                    |                    |
| subjects affected / exposed | 0 / 199 (0.00%)    | 1 / 199 (0.50%)    |
| occurrences (all)           | 0                  | 1                  |

|                                       |                   |                   |
|---------------------------------------|-------------------|-------------------|
| General clinical conditions worsening |                   |                   |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                     | 1                 | 0                 |
| General status alteration             |                   |                   |
| subjects affected / exposed           | 3 / 199 (1.51%)   | 0 / 199 (0.00%)   |
| occurrences (all)                     | 3                 | 0                 |
| General weakness                      |                   |                   |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                     | 1                 | 0                 |
| Generalized edema                     |                   |                   |
| subjects affected / exposed           | 0 / 199 (0.00%)   | 4 / 199 (2.01%)   |
| occurrences (all)                     | 0                 | 4                 |
| Gout                                  |                   |                   |
| subjects affected / exposed           | 2 / 199 (1.01%)   | 1 / 199 (0.50%)   |
| occurrences (all)                     | 2                 | 1                 |
| Hypersalivation                       |                   |                   |
| subjects affected / exposed           | 0 / 199 (0.00%)   | 2 / 199 (1.01%)   |
| occurrences (all)                     | 0                 | 2                 |
| Infusion site extravasation           |                   |                   |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                     | 1                 | 0                 |
| Injection site reaction               |                   |                   |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                     | 1                 | 0                 |
| Localized edema                       |                   |                   |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |
| occurrences (all)                     | 1                 | 1                 |
| Malaise                               |                   |                   |
| subjects affected / exposed           | 4 / 199 (2.01%)   | 4 / 199 (2.01%)   |
| occurrences (all)                     | 4                 | 4                 |
| Metallic taste                        |                   |                   |
| subjects affected / exposed           | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)                     | 0                 | 1                 |
| Non-cardiac chest pain                |                   |                   |
| subjects affected / exposed           | 31 / 199 (15.58%) | 36 / 199 (18.09%) |
| occurrences (all)                     | 31                | 36                |

|                                          |                  |                   |  |
|------------------------------------------|------------------|-------------------|--|
| Pain                                     |                  |                   |  |
| subjects affected / exposed              | 14 / 199 (7.04%) | 21 / 199 (10.55%) |  |
| occurrences (all)                        | 14               | 21                |  |
| Penis red lesions                        |                  |                   |  |
| subjects affected / exposed              | 0 / 199 (0.00%)  | 1 / 199 (0.50%)   |  |
| occurrences (all)                        | 0                | 1                 |  |
| Proximal myopathy                        |                  |                   |  |
| subjects affected / exposed              | 0 / 199 (0.00%)  | 1 / 199 (0.50%)   |  |
| occurrences (all)                        | 0                | 1                 |  |
| Tingling knee                            |                  |                   |  |
| subjects affected / exposed              | 1 / 199 (0.50%)  | 0 / 199 (0.00%)   |  |
| occurrences (all)                        | 1                | 0                 |  |
| Cholestasis                              |                  |                   |  |
| subjects affected / exposed              | 0 / 199 (0.00%)  | 1 / 199 (0.50%)   |  |
| occurrences (all)                        | 0                | 1                 |  |
| Immune system disorders                  |                  |                   |  |
| Allergic reaction                        |                  |                   |  |
| subjects affected / exposed              | 5 / 199 (2.51%)  | 2 / 199 (1.01%)   |  |
| occurrences (all)                        | 5                | 2                 |  |
| Polymyalgia rheumatica-like syndrome     |                  |                   |  |
| subjects affected / exposed              | 1 / 199 (0.50%)  | 0 / 199 (0.00%)   |  |
| occurrences (all)                        | 1                | 0                 |  |
| Social circumstances                     |                  |                   |  |
| Reduced mobility                         |                  |                   |  |
| subjects affected / exposed              | 1 / 199 (0.50%)  | 0 / 199 (0.00%)   |  |
| occurrences (all)                        | 1                | 0                 |  |
| Split lip                                |                  |                   |  |
| subjects affected / exposed              | 1 / 199 (0.50%)  | 0 / 199 (0.00%)   |  |
| occurrences (all)                        | 1                | 0                 |  |
| Reproductive system and breast disorders |                  |                   |  |
| Erectile dysfunction                     |                  |                   |  |
| subjects affected / exposed              | 1 / 199 (0.50%)  | 0 / 199 (0.00%)   |  |
| occurrences (all)                        | 1                | 0                 |  |
| Genital edema                            |                  |                   |  |
| subjects affected / exposed              | 0 / 199 (0.00%)  | 1 / 199 (0.50%)   |  |
| occurrences (all)                        | 0                | 1                 |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| Gynecomastia                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                               | 1                 | 1                 |  |
| Pelvic pain                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                               | 1                 | 0                 |  |
| Penile pain                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                               | 1                 | 0                 |  |
| Prostate hypertrophy                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                               | 1                 | 0                 |  |
| Testicular swelling                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                               | 1                 | 0                 |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Allergic rhinitis                               |                   |                   |  |
| subjects affected / exposed                     | 6 / 199 (3.02%)   | 3 / 199 (1.51%)   |  |
| occurrences (all)                               | 6                 | 3                 |  |
| Bloody sputum                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                               | 0                 | 1                 |  |
| Bronchial obstruction                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                               | 1                 | 0                 |  |
| Bronchopulmonary hemorrhage                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                               | 1                 | 0                 |  |
| Bronchospasm                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 199 (0.00%)   | 2 / 199 (1.01%)   |  |
| occurrences (all)                               | 0                 | 2                 |  |
| Cough                                           |                   |                   |  |
| subjects affected / exposed                     | 33 / 199 (16.58%) | 32 / 199 (16.08%) |  |
| occurrences (all)                               | 33                | 32                |  |
| Dry nasal                                       |                   |                   |  |

|                               |                   |                   |
|-------------------------------|-------------------|-------------------|
| subjects affected / exposed   | 1 / 199 (0.50%)   | 2 / 199 (1.01%)   |
| occurrences (all)             | 1                 | 2                 |
| Dry nose                      |                   |                   |
| subjects affected / exposed   | 0 / 199 (0.00%)   | 2 / 199 (1.01%)   |
| occurrences (all)             | 0                 | 2                 |
| Dyspnea                       |                   |                   |
| subjects affected / exposed   | 38 / 199 (19.10%) | 47 / 199 (23.62%) |
| occurrences (all)             | 38                | 47                |
| Epistaxis                     |                   |                   |
| subjects affected / exposed   | 56 / 199 (28.14%) | 56 / 199 (28.14%) |
| occurrences (all)             | 56                | 56                |
| Hemoptysis                    |                   |                   |
| subjects affected / exposed   | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |
| occurrences (all)             | 1                 | 1                 |
| Hiccups                       |                   |                   |
| subjects affected / exposed   | 2 / 199 (1.01%)   | 5 / 199 (2.51%)   |
| occurrences (all)             | 2                 | 5                 |
| Hoarseness                    |                   |                   |
| subjects affected / exposed   | 11 / 199 (5.53%)  | 9 / 199 (4.52%)   |
| occurrences (all)             | 11                | 9                 |
| Hypoxia                       |                   |                   |
| subjects affected / exposed   | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)             | 0                 | 1                 |
| Interstitial lung infiltrates |                   |                   |
| subjects affected / exposed   | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)             | 0                 | 1                 |
| Laryngeal inflammation        |                   |                   |
| subjects affected / exposed   | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)             | 1                 | 0                 |
| Laryngeal mucositis           |                   |                   |
| subjects affected / exposed   | 1 / 199 (0.50%)   | 2 / 199 (1.01%)   |
| occurrences (all)             | 1                 | 2                 |
| Nasal congestion              |                   |                   |
| subjects affected / exposed   | 2 / 199 (1.01%)   | 5 / 199 (2.51%)   |
| occurrences (all)             | 2                 | 5                 |
| Nocturnal mucus               |                   |                   |

|                                      |                 |                  |
|--------------------------------------|-----------------|------------------|
| subjects affected / exposed          | 0 / 199 (0.00%) | 1 / 199 (0.50%)  |
| occurrences (all)                    | 0               | 1                |
| Oropharyngeal pain                   |                 |                  |
| subjects affected / exposed          | 0 / 199 (0.00%) | 1 / 199 (0.50%)  |
| occurrences (all)                    | 0               | 1                |
| Pharyngeal mucositis                 |                 |                  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 1 / 199 (0.50%)  |
| occurrences (all)                    | 1               | 1                |
| Pharyngolaryngeal pain               |                 |                  |
| subjects affected / exposed          | 2 / 199 (1.01%) | 0 / 199 (0.00%)  |
| occurrences (all)                    | 2               | 0                |
| Phlegm                               |                 |                  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 1 / 199 (0.50%)  |
| occurrences (all)                    | 1               | 1                |
| Pleural drainage insertion site pain |                 |                  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 0 / 199 (0.00%)  |
| occurrences (all)                    | 1               | 0                |
| Pleural effusion                     |                 |                  |
| subjects affected / exposed          | 3 / 199 (1.51%) | 2 / 199 (1.01%)  |
| occurrences (all)                    | 3               | 2                |
| Pleuritic pain                       |                 |                  |
| subjects affected / exposed          | 5 / 199 (2.51%) | 10 / 199 (5.03%) |
| occurrences (all)                    | 5               | 10               |
| Pneumonitis                          |                 |                  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 3 / 199 (1.51%)  |
| occurrences (all)                    | 1               | 3                |
| Pneumothorax                         |                 |                  |
| subjects affected / exposed          | 2 / 199 (1.01%) | 1 / 199 (0.50%)  |
| occurrences (all)                    | 2               | 1                |
| Postnasal drip                       |                 |                  |
| subjects affected / exposed          | 3 / 199 (1.51%) | 0 / 199 (0.00%)  |
| occurrences (all)                    | 3               | 0                |
| Productive cough                     |                 |                  |
| subjects affected / exposed          | 4 / 199 (2.01%) | 5 / 199 (2.51%)  |
| occurrences (all)                    | 4               | 5                |
| Pulmonary edema                      |                 |                  |

|                                                  |                        |                        |  |
|--------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 199 (0.50%)<br>1   | 1 / 199 (0.50%)<br>1   |  |
| Rhinorrhea                                       |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 11 / 199 (5.53%)<br>11 | 17 / 199 (8.54%)<br>17 |  |
| Sinus disorder                                   |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 199 (0.50%)<br>1   | 2 / 199 (1.01%)<br>2   |  |
| Sore throat                                      |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 5 / 199 (2.51%)<br>5   | 3 / 199 (1.51%)<br>3   |  |
| Voice alteration                                 |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 6 / 199 (3.02%)<br>6   | 8 / 199 (4.02%)<br>8   |  |
| Wheezing                                         |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 199 (1.01%)<br>2   | 1 / 199 (0.50%)<br>1   |  |
| Psychiatric disorders                            |                        |                        |  |
| Agitation                                        |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 199 (2.01%)<br>4   | 2 / 199 (1.01%)<br>2   |  |
| Anxiety                                          |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 9 / 199 (4.52%)<br>9   | 9 / 199 (4.52%)<br>9   |  |
| Conduct disorder                                 |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 199 (0.50%)<br>1   | 0 / 199 (0.00%)<br>0   |  |
| Confusion                                        |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 199 (0.50%)<br>1   | 2 / 199 (1.01%)<br>2   |  |
| Delirium                                         |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 199 (0.00%)<br>0   | 1 / 199 (0.50%)<br>1   |  |
| Depression                                       |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 6 / 199 (3.02%)<br>6   | 11 / 199 (5.53%)<br>11 |  |

|                                       |                   |                   |  |
|---------------------------------------|-------------------|-------------------|--|
| Insomnia                              |                   |                   |  |
| subjects affected / exposed           | 19 / 199 (9.55%)  | 16 / 199 (8.04%)  |  |
| occurrences (all)                     | 19                | 16                |  |
| Irritability                          |                   |                   |  |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                     | 1                 | 0                 |  |
| Libido increased                      |                   |                   |  |
| subjects affected / exposed           | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                     | 0                 | 1                 |  |
| Mood change                           |                   |                   |  |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                     | 1                 | 0                 |  |
| Nightmares                            |                   |                   |  |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                     | 1                 | 0                 |  |
| Investigations                        |                   |                   |  |
| Alanine aminotransferase increased    |                   |                   |  |
| subjects affected / exposed           | 26 / 199 (13.07%) | 25 / 199 (12.56%) |  |
| occurrences (all)                     | 26                | 25                |  |
| Alkaline phosphatase increased        |                   |                   |  |
| subjects affected / exposed           | 6 / 199 (3.02%)   | 6 / 199 (3.02%)   |  |
| occurrences (all)                     | 6                 | 6                 |  |
| Aspartate aminotransferase increased  |                   |                   |  |
| subjects affected / exposed           | 24 / 199 (12.06%) | 21 / 199 (10.55%) |  |
| occurrences (all)                     | 24                | 21                |  |
| Blood bilirubin increased             |                   |                   |  |
| subjects affected / exposed           | 3 / 199 (1.51%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                     | 3                 | 1                 |  |
| Blood corticotrophin decreased        |                   |                   |  |
| subjects affected / exposed           | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                     | 0                 | 1                 |  |
| Blood lactate dehydrogenase increased |                   |                   |  |
| subjects affected / exposed           | 5 / 199 (2.51%)   | 2 / 199 (1.01%)   |  |
| occurrences (all)                     | 5                 | 2                 |  |
| C-reactive protein increased          |                   |                   |  |

|                                                   |                   |                   |
|---------------------------------------------------|-------------------|-------------------|
| subjects affected / exposed                       | 3 / 199 (1.51%)   | 2 / 199 (1.01%)   |
| occurrences (all)                                 | 3                 | 2                 |
| CPK increased                                     |                   |                   |
| subjects affected / exposed                       | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                 | 1                 | 0                 |
| Cardiac troponin T increased                      |                   |                   |
| subjects affected / exposed                       | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)                                 | 0                 | 1                 |
| Cholesterol high                                  |                   |                   |
| subjects affected / exposed                       | 5 / 199 (2.51%)   | 1 / 199 (0.50%)   |
| occurrences (all)                                 | 5                 | 1                 |
| Creatinine decreased                              |                   |                   |
| subjects affected / exposed                       | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)                                 | 0                 | 1                 |
| Creatinine increased                              |                   |                   |
| subjects affected / exposed                       | 39 / 199 (19.60%) | 24 / 199 (12.06%) |
| occurrences (all)                                 | 39                | 24                |
| Electrocardiogram QT corrected interval prolonged |                   |                   |
| subjects affected / exposed                       | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)                                 | 0                 | 1                 |
| GGT increased                                     |                   |                   |
| subjects affected / exposed                       | 14 / 199 (7.04%)  | 15 / 199 (7.54%)  |
| occurrences (all)                                 | 14                | 15                |
| Hemoglobin increased                              |                   |                   |
| subjects affected / exposed                       | 2 / 199 (1.01%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                 | 2                 | 0                 |
| INR increased                                     |                   |                   |
| subjects affected / exposed                       | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |
| occurrences (all)                                 | 1                 | 1                 |
| Iron deficiency                                   |                   |                   |
| subjects affected / exposed                       | 1 / 199 (0.50%)   | 2 / 199 (1.01%)   |
| occurrences (all)                                 | 1                 | 2                 |
| Lipase increased                                  |                   |                   |
| subjects affected / exposed                       | 7 / 199 (3.52%)   | 6 / 199 (3.02%)   |
| occurrences (all)                                 | 7                 | 6                 |

|                                                                                                  |                         |                         |
|--------------------------------------------------------------------------------------------------|-------------------------|-------------------------|
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 199 (2.01%)<br>4    | 4 / 199 (2.01%)<br>4    |
| Lymphocyte count increased<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                   | 63 / 199 (31.66%)<br>63 | 56 / 199 (28.14%)<br>56 |
| Neutrophil count increased<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 199 (0.00%)<br>0    | 1 / 199 (0.50%)<br>1    |
| Pancreatic amylase<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                     | 39 / 199 (19.60%)<br>39 | 24 / 199 (12.06%)<br>24 |
| Platelet count increased<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |
| Prostate-specific antigen (PSA)<br>increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |
| Serum amylase increased<br>subjects affected / exposed<br>occurrences (all)                      | 16 / 199 (8.04%)<br>16  | 13 / 199 (6.53%)<br>13  |
| Serum urea increased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |
| Thyroid stimulating hormone<br>increased<br>subjects affected / exposed<br>occurrences (all)     | 5 / 199 (2.51%)<br>5    | 1 / 199 (0.50%)<br>1    |
| Urea increased                                                                                   |                         |                         |

|                                                                                |                        |                        |  |
|--------------------------------------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                               | 0 / 199 (0.00%)<br>0   | 1 / 199 (0.50%)<br>1   |  |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all)       | 1 / 199 (0.50%)<br>1   | 0 / 199 (0.00%)<br>0   |  |
| Weight gain<br>subjects affected / exposed<br>occurrences (all)                | 1 / 199 (0.50%)<br>1   | 1 / 199 (0.50%)<br>1   |  |
| Weight loss<br>subjects affected / exposed<br>occurrences (all)                | 15 / 199 (7.54%)<br>15 | 11 / 199 (5.53%)<br>11 |  |
| White blood cell decreased<br>subjects affected / exposed<br>occurrences (all) | 14 / 199 (7.04%)<br>14 | 9 / 199 (4.52%)<br>9   |  |
| Hypoglycemia<br>subjects affected / exposed<br>occurrences (all)               | 1 / 199 (0.50%)<br>1   | 2 / 199 (1.01%)<br>2   |  |
| Injury, poisoning and procedural complications                                 |                        |                        |  |
| Bruising<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 199 (1.01%)<br>2   | 3 / 199 (1.51%)<br>3   |  |
| Burn<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 199 (0.00%)<br>0   | 1 / 199 (0.50%)<br>1   |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                       | 5 / 199 (2.51%)<br>5   | 1 / 199 (0.50%)<br>1   |  |
| Fracture<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 199 (0.50%)<br>1   | 2 / 199 (1.01%)<br>2   |  |
| Infusion related reaction<br>subjects affected / exposed<br>occurrences (all)  | 15 / 199 (7.54%)<br>15 | 3 / 199 (1.51%)<br>3   |  |
| Port dehiscence                                                                |                        |                        |  |

|                                                   |                 |                 |  |
|---------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                       | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                 | 0               | 1               |  |
| Spinal fracture                                   |                 |                 |  |
| subjects affected / exposed                       | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                 | 1               | 0               |  |
| Tick bite                                         |                 |                 |  |
| subjects affected / exposed                       | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                 | 1               | 0               |  |
| Vascular access complication                      |                 |                 |  |
| subjects affected / exposed                       | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                 | 1               | 0               |  |
| Cardiac disorders                                 |                 |                 |  |
| Atrial fibrillation                               |                 |                 |  |
| subjects affected / exposed                       | 3 / 199 (1.51%) | 6 / 199 (3.02%) |  |
| occurrences (all)                                 | 3               | 6               |  |
| Atrial flutter                                    |                 |                 |  |
| subjects affected / exposed                       | 0 / 199 (0.00%) | 3 / 199 (1.51%) |  |
| occurrences (all)                                 | 0               | 3               |  |
| Automatic defibrillator implantation (accidental) |                 |                 |  |
| subjects affected / exposed                       | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                 | 1               | 0               |  |
| Chest pain - cardiac                              |                 |                 |  |
| subjects affected / exposed                       | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                 | 2               | 0               |  |
| Heart failure                                     |                 |                 |  |
| subjects affected / exposed                       | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                 | 1               | 0               |  |
| Palpitations                                      |                 |                 |  |
| subjects affected / exposed                       | 2 / 199 (1.01%) | 2 / 199 (1.01%) |  |
| occurrences (all)                                 | 2               | 2               |  |
| Paroxysmal auricular fibrillation                 |                 |                 |  |
| subjects affected / exposed                       | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                 | 1               | 0               |  |
| Pericardial effusion                              |                 |                 |  |

|                                                                                                            |                      |                      |  |
|------------------------------------------------------------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                           | 1 / 199 (0.50%)<br>1 | 1 / 199 (0.50%)<br>1 |  |
| Sinus bradycardia<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 199 (1.01%)<br>2 | 2 / 199 (1.01%)<br>2 |  |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 199 (0.50%)<br>1 | 7 / 199 (3.52%)<br>7 |  |
| Supraventricular tachycardia<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 199 (0.00%)<br>0 | 1 / 199 (0.50%)<br>1 |  |
| Nervous system disorders                                                                                   |                      |                      |  |
| Acute flaccid paraparesis (from the<br>clavicles down)<br>subjects affected / exposed<br>occurrences (all) | 0 / 199 (0.00%)<br>0 | 1 / 199 (0.50%)<br>1 |  |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)                                                | 1 / 199 (0.50%)<br>1 | 0 / 199 (0.00%)<br>0 |  |
| Anosmia<br>subjects affected / exposed<br>occurrences (all)                                                | 2 / 199 (1.01%)<br>2 | 0 / 199 (0.00%)<br>0 |  |
| Balance issues<br>subjects affected / exposed<br>occurrences (all)                                         | 0 / 199 (0.00%)<br>0 | 1 / 199 (0.50%)<br>1 |  |
| Cognitive disturbance<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 199 (0.50%)<br>1 | 0 / 199 (0.00%)<br>0 |  |
| Concentration impairment<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 199 (0.00%)<br>0 | 1 / 199 (0.50%)<br>1 |  |
| Depressed level of consciousness<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 199 (0.50%)<br>1 | 0 / 199 (0.00%)<br>0 |  |
| Dizziness                                                                                                  |                      |                      |  |

|                             |                   |                   |
|-----------------------------|-------------------|-------------------|
| subjects affected / exposed | 8 / 199 (4.02%)   | 12 / 199 (6.03%)  |
| occurrences (all)           | 8                 | 12                |
| Dysesthesia                 |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 1                 | 1                 |
| Dysgeusia                   |                   |                   |
| subjects affected / exposed | 27 / 199 (13.57%) | 17 / 199 (8.54%)  |
| occurrences (all)           | 27                | 17                |
| Faint                       |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Headache                    |                   |                   |
| subjects affected / exposed | 23 / 199 (11.56%) | 22 / 199 (11.06%) |
| occurrences (all)           | 23                | 22                |
| Ischemia cerebrovascular    |                   |                   |
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 0                 | 1                 |
| Lethargy                    |                   |                   |
| subjects affected / exposed | 5 / 199 (2.51%)   | 2 / 199 (1.01%)   |
| occurrences (all)           | 5                 | 2                 |
| Memory impairment           |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 1                 | 1                 |
| Movements involuntary       |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Neuralgia                   |                   |                   |
| subjects affected / exposed | 2 / 199 (1.01%)   | 2 / 199 (1.01%)   |
| occurrences (all)           | 2                 | 2                 |
| Nystagmus                   |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Paresthesia                 |                   |                   |
| subjects affected / exposed | 5 / 199 (2.51%)   | 4 / 199 (2.01%)   |
| occurrences (all)           | 5                 | 4                 |
| Peripheral motor neuropathy |                   |                   |

|                                      |                 |                 |  |
|--------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed          | 2 / 199 (1.01%) | 3 / 199 (1.51%) |  |
| occurrences (all)                    | 2               | 3               |  |
| Peripheral sensory neuropathy        |                 |                 |  |
| subjects affected / exposed          | 8 / 199 (4.02%) | 2 / 199 (1.01%) |  |
| occurrences (all)                    | 8               | 2               |  |
| Presyncope                           |                 |                 |  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                    | 1               | 0               |  |
| Ride instability                     |                 |                 |  |
| subjects affected / exposed          | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                    | 0               | 1               |  |
| Seizure                              |                 |                 |  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                    | 1               | 0               |  |
| Somnolence                           |                 |                 |  |
| subjects affected / exposed          | 2 / 199 (1.01%) | 1 / 199 (0.50%) |  |
| occurrences (all)                    | 2               | 1               |  |
| Spasticity                           |                 |                 |  |
| subjects affected / exposed          | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                    | 0               | 1               |  |
| Syncope                              |                 |                 |  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                    | 1               | 0               |  |
| Torticollis                          |                 |                 |  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                    | 1               | 0               |  |
| Tremor                               |                 |                 |  |
| subjects affected / exposed          | 3 / 199 (1.51%) | 2 / 199 (1.01%) |  |
| occurrences (all)                    | 3               | 2               |  |
| Trigeminal nerve disorder            |                 |                 |  |
| subjects affected / exposed          | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences (all)                    | 2               | 0               |  |
| Vasovagal reaction                   |                 |                 |  |
| subjects affected / exposed          | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences (all)                    | 1               | 1               |  |
| Blood and lymphatic system disorders |                 |                 |  |

|                                     |                   |                   |  |
|-------------------------------------|-------------------|-------------------|--|
| Anemia                              |                   |                   |  |
| subjects affected / exposed         | 68 / 199 (34.17%) | 69 / 199 (34.67%) |  |
| occurrences (all)                   | 68                | 69                |  |
| Cytolysis Eosinophilia              |                   |                   |  |
| subjects affected / exposed         | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 0                 | 1                 |  |
| Febrile neutropenia                 |                   |                   |  |
| subjects affected / exposed         | 6 / 199 (3.02%)   | 3 / 199 (1.51%)   |  |
| occurrences (all)                   | 6                 | 3                 |  |
| Hemolysis                           |                   |                   |  |
| subjects affected / exposed         | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 0                 | 1                 |  |
| Hypovolemic shock                   |                   |                   |  |
| subjects affected / exposed         | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                   | 1                 | 0                 |  |
| Leukocytosis                        |                   |                   |  |
| subjects affected / exposed         | 2 / 199 (1.01%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                   | 2                 | 0                 |  |
| Lymph node pain                     |                   |                   |  |
| subjects affected / exposed         | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 0                 | 1                 |  |
| Neutrophilia                        |                   |                   |  |
| subjects affected / exposed         | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                   | 1                 | 0                 |  |
| Thrombocytosis                      |                   |                   |  |
| subjects affected / exposed         | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 0                 | 1                 |  |
| Thrombotic thrombocytopenic purpura |                   |                   |  |
| subjects affected / exposed         | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                   | 1                 | 0                 |  |
| Ear and labyrinth disorders         |                   |                   |  |
| Ear discharge (right)               |                   |                   |  |
| subjects affected / exposed         | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)                   | 0                 | 1                 |  |
| Ear pain                            |                   |                   |  |

|                                                                                            |                        |                      |  |
|--------------------------------------------------------------------------------------------|------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                           | 1 / 199 (0.50%)<br>1   | 1 / 199 (0.50%)<br>1 |  |
| Hearing impaired<br>subjects affected / exposed<br>occurrences (all)                       | 3 / 199 (1.51%)<br>3   | 1 / 199 (0.50%)<br>1 |  |
| Hyperacusis<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 199 (0.00%)<br>0   | 1 / 199 (0.50%)<br>1 |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 199 (1.01%)<br>2   | 4 / 199 (2.01%)<br>4 |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                                | 5 / 199 (2.51%)<br>5   | 3 / 199 (1.51%)<br>3 |  |
| Eye disorders<br>(Hyper)sensitive eyes<br>subjects affected / exposed<br>occurrences (all) | 2 / 199 (1.01%)<br>2   | 0 / 199 (0.00%)<br>0 |  |
| Blurred vision<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 199 (1.01%)<br>2   | 2 / 199 (1.01%)<br>2 |  |
| Cataract<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 199 (1.01%)<br>2   | 1 / 199 (0.50%)<br>1 |  |
| Diplopia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 199 (0.00%)<br>0   | 1 / 199 (0.50%)<br>1 |  |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)                                | 12 / 199 (6.03%)<br>12 | 7 / 199 (3.52%)<br>7 |  |
| Eye discharge<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 199 (0.00%)<br>0   | 1 / 199 (0.50%)<br>1 |  |
| Eye herpes (right)<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 199 (0.00%)<br>0   | 1 / 199 (0.50%)<br>1 |  |

|                                     |                 |                 |
|-------------------------------------|-----------------|-----------------|
| Eye irritation                      |                 |                 |
| subjects affected / exposed         | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)                   | 1               | 0               |
| Eye pain                            |                 |                 |
| subjects affected / exposed         | 2 / 199 (1.01%) | 0 / 199 (0.00%) |
| occurrences (all)                   | 2               | 0               |
| Eyelid function disorder            |                 |                 |
| subjects affected / exposed         | 0 / 199 (0.00%) | 1 / 199 (0.50%) |
| occurrences (all)                   | 0               | 1               |
| Flashing lights                     |                 |                 |
| subjects affected / exposed         | 0 / 199 (0.00%) | 2 / 199 (1.01%) |
| occurrences (all)                   | 0               | 2               |
| Floaters                            |                 |                 |
| subjects affected / exposed         | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)                   | 1               | 0               |
| Full thickness macular hole (right) |                 |                 |
| subjects affected / exposed         | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)                   | 1               | 0               |
| Glaucoma                            |                 |                 |
| subjects affected / exposed         | 0 / 199 (0.00%) | 1 / 199 (0.50%) |
| occurrences (all)                   | 0               | 1               |
| Gritty eyes                         |                 |                 |
| subjects affected / exposed         | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)                   | 1               | 0               |
| Hyperopia                           |                 |                 |
| subjects affected / exposed         | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)                   | 1               | 0               |
| Hyposfagma (right eye)              |                 |                 |
| subjects affected / exposed         | 0 / 199 (0.00%) | 1 / 199 (0.50%) |
| occurrences (all)                   | 0               | 1               |
| Inferotemporal nevus eye (left)     |                 |                 |
| subjects affected / exposed         | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)                   | 1               | 0               |
| Keratitis                           |                 |                 |
| subjects affected / exposed         | 0 / 199 (0.00%) | 1 / 199 (0.50%) |
| occurrences (all)                   | 0               | 1               |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| Redness eye (left)          |                   |                   |  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)           | 1                 | 0                 |  |
| Vision decreased            |                   |                   |  |
| subjects affected / exposed | 0 / 199 (0.00%)   | 2 / 199 (1.01%)   |  |
| occurrences (all)           | 0                 | 2                 |  |
| Visual acuity loss          |                   |                   |  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)           | 1                 | 1                 |  |
| Visual impairment           |                   |                   |  |
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)           | 0                 | 1                 |  |
| Watering eyes               |                   |                   |  |
| subjects affected / exposed | 17 / 199 (8.54%)  | 25 / 199 (12.56%) |  |
| occurrences (all)           | 17                | 25                |  |
| Gastrointestinal disorders  |                   |                   |  |
| Abdomen sensibility         |                   |                   |  |
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)           | 0                 | 1                 |  |
| Abdominal cramps            |                   |                   |  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)           | 1                 | 0                 |  |
| Abdominal distension        |                   |                   |  |
| subjects affected / exposed | 2 / 199 (1.01%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)           | 2                 | 0                 |  |
| Abdominal pain              |                   |                   |  |
| subjects affected / exposed | 22 / 199 (11.06%) | 15 / 199 (7.54%)  |  |
| occurrences (all)           | 22                | 15                |  |
| Anal fissure                |                   |                   |  |
| subjects affected / exposed | 2 / 199 (1.01%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)           | 2                 | 0                 |  |
| Anal fistula                |                   |                   |  |
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |  |
| occurrences (all)           | 0                 | 1                 |  |
| Anal hemorrhage             |                   |                   |  |

|                             |                   |                   |
|-----------------------------|-------------------|-------------------|
| subjects affected / exposed | 3 / 199 (1.51%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 3                 | 1                 |
| Anal mucositis              |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 1                 | 1                 |
| Anal pain                   |                   |                   |
| subjects affected / exposed | 0 / 199 (0.00%)   | 2 / 199 (1.01%)   |
| occurrences (all)           | 0                 | 2                 |
| Ascites                     |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 1                 | 1                 |
| Belching                    |                   |                   |
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 0                 | 1                 |
| Bloating                    |                   |                   |
| subjects affected / exposed | 2 / 199 (1.01%)   | 2 / 199 (1.01%)   |
| occurrences (all)           | 2                 | 2                 |
| Colitis                     |                   |                   |
| subjects affected / exposed | 6 / 199 (3.02%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 6                 | 1                 |
| Constipation                |                   |                   |
| subjects affected / exposed | 82 / 199 (41.21%) | 80 / 199 (40.20%) |
| occurrences (all)           | 82                | 80                |
| Dental caries               |                   |                   |
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 0                 | 1                 |
| Diarrhea                    |                   |                   |
| subjects affected / exposed | 55 / 199 (27.64%) | 39 / 199 (19.60%) |
| occurrences (all)           | 55                | 39                |
| Diverticulitis              |                   |                   |
| subjects affected / exposed | 3 / 199 (1.51%)   | 0 / 199 (0.00%)   |
| occurrences (all)           | 3                 | 0                 |
| Dry mouth                   |                   |                   |
| subjects affected / exposed | 8 / 199 (4.02%)   | 8 / 199 (4.02%)   |
| occurrences (all)           | 8                 | 8                 |
| Dyspepsia                   |                   |                   |

|                                 |                 |                  |
|---------------------------------|-----------------|------------------|
| subjects affected / exposed     | 7 / 199 (3.52%) | 7 / 199 (3.52%)  |
| occurrences (all)               | 7               | 7                |
| Dysphagia                       |                 |                  |
| subjects affected / exposed     | 9 / 199 (4.52%) | 8 / 199 (4.02%)  |
| occurrences (all)               | 9               | 8                |
| Epigastralgia                   |                 |                  |
| subjects affected / exposed     | 1 / 199 (0.50%) | 0 / 199 (0.00%)  |
| occurrences (all)               | 1               | 0                |
| Esophageal pain                 |                 |                  |
| subjects affected / exposed     | 0 / 199 (0.00%) | 1 / 199 (0.50%)  |
| occurrences (all)               | 0               | 1                |
| Fecal incontinence              |                 |                  |
| subjects affected / exposed     | 0 / 199 (0.00%) | 1 / 199 (0.50%)  |
| occurrences (all)               | 0               | 1                |
| Flatulence                      |                 |                  |
| subjects affected / exposed     | 1 / 199 (0.50%) | 2 / 199 (1.01%)  |
| occurrences (all)               | 1               | 2                |
| Food poisoning                  |                 |                  |
| subjects affected / exposed     | 0 / 199 (0.00%) | 1 / 199 (0.50%)  |
| occurrences (all)               | 0               | 1                |
| Gastric hemorrhage              |                 |                  |
| subjects affected / exposed     | 0 / 199 (0.00%) | 1 / 199 (0.50%)  |
| occurrences (all)               | 0               | 1                |
| Gastric ulcer                   |                 |                  |
| subjects affected / exposed     | 1 / 199 (0.50%) | 1 / 199 (0.50%)  |
| occurrences (all)               | 1               | 1                |
| Gastritis                       |                 |                  |
| subjects affected / exposed     | 5 / 199 (2.51%) | 2 / 199 (1.01%)  |
| occurrences (all)               | 5               | 2                |
| Gastroesophageal reflux disease |                 |                  |
| subjects affected / exposed     | 8 / 199 (4.02%) | 11 / 199 (5.53%) |
| occurrences (all)               | 8               | 11               |
| Gastrointestinal pain           |                 |                  |
| subjects affected / exposed     | 2 / 199 (1.01%) | 4 / 199 (2.01%)  |
| occurrences (all)               | 2               | 4                |
| Gingival hyperplasia            |                 |                  |

|                             |                   |                   |
|-----------------------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 0                 | 1                 |
| Gingival pain               |                   |                   |
| subjects affected / exposed | 2 / 199 (1.01%)   | 2 / 199 (1.01%)   |
| occurrences (all)           | 2                 | 2                 |
| Glossitis                   |                   |                   |
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 0                 | 1                 |
| Hemorrhoidal hemorrhage     |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 1                 | 1                 |
| Hemorrhoids                 |                   |                   |
| subjects affected / exposed | 7 / 199 (3.52%)   | 7 / 199 (3.52%)   |
| occurrences (all)           | 7                 | 7                 |
| Hernia                      |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Hiatus hernia               |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Inguinal hernia             |                   |                   |
| subjects affected / exposed | 2 / 199 (1.01%)   | 0 / 199 (0.00%)   |
| occurrences (all)           | 2                 | 0                 |
| Mouth sores                 |                   |                   |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Mouth ulcer                 |                   |                   |
| subjects affected / exposed | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)           | 0                 | 1                 |
| Mucositis oral              |                   |                   |
| subjects affected / exposed | 65 / 199 (32.66%) | 47 / 199 (23.62%) |
| occurrences (all)           | 65                | 47                |
| Nausea                      |                   |                   |
| subjects affected / exposed | 84 / 199 (42.21%) | 93 / 199 (46.73%) |
| occurrences (all)           | 84                | 93                |
| Odynophagia                 |                   |                   |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Oral dysesthesia            |                 |                 |
| subjects affected / exposed | 2 / 199 (1.01%) | 0 / 199 (0.00%) |
| occurrences (all)           | 2               | 0               |
| Oral hemorrhage             |                 |                 |
| subjects affected / exposed | 3 / 199 (1.51%) | 2 / 199 (1.01%) |
| occurrences (all)           | 3               | 2               |
| Oral pain                   |                 |                 |
| subjects affected / exposed | 5 / 199 (2.51%) | 1 / 199 (0.50%) |
| occurrences (all)           | 5               | 1               |
| Pancreatitis                |                 |                 |
| subjects affected / exposed | 1 / 199 (0.50%) | 1 / 199 (0.50%) |
| occurrences (all)           | 1               | 1               |
| Periodontal disease         |                 |                 |
| subjects affected / exposed | 5 / 199 (2.51%) | 0 / 199 (0.00%) |
| occurrences (all)           | 5               | 0               |
| Proctitis                   |                 |                 |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 199 (0.50%) |
| occurrences (all)           | 0               | 1               |
| Pyrosis                     |                 |                 |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Rectal hemorrhage           |                 |                 |
| subjects affected / exposed | 4 / 199 (2.01%) | 2 / 199 (1.01%) |
| occurrences (all)           | 4               | 2               |
| Rectal pain                 |                 |                 |
| subjects affected / exposed | 2 / 199 (1.01%) | 0 / 199 (0.00%) |
| occurrences (all)           | 2               | 0               |
| Retching                    |                 |                 |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Salivary duct inflammation  |                 |                 |
| subjects affected / exposed | 1 / 199 (0.50%) | 1 / 199 (0.50%) |
| occurrences (all)           | 1               | 1               |
| Stomach pain                |                 |                 |

|                                                                                                                                |                         |                         |  |
|--------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                               | 6 / 199 (3.02%)<br>6    | 5 / 199 (2.51%)<br>5    |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                                                 | 2 / 199 (1.01%)<br>2    | 0 / 199 (0.00%)<br>0    |  |
| Teeth sensibility<br>subjects affected / exposed<br>occurrences (all)                                                          | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                                                                  | 7 / 199 (3.52%)<br>7    | 1 / 199 (0.50%)<br>1    |  |
| Umbilical hernia<br>subjects affected / exposed<br>occurrences (all)                                                           | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |  |
| Upper gastrointestinal hemorrhage<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                                   | 30 / 199 (15.08%)<br>30 | 28 / 199 (14.07%)<br>28 |  |
| Hepatobiliary disorders<br>Cholangitis<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |  |
| Hepatic pain<br>subjects affected / exposed<br>occurrences (all)                                                               | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |  |
| Intrahepatic bile ducts/common bile<br>duct dilatation<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 199 (0.00%)<br>0    | 1 / 199 (0.50%)<br>1    |  |
| Skin and subcutaneous tissue disorders<br>Actinic keratosis eyelid (right)<br>subjects affected / exposed<br>occurrences (all) | 1 / 199 (0.50%)<br>1    | 0 / 199 (0.00%)<br>0    |  |
| Alopecia                                                                                                                       |                         |                         |  |

|                                     |                  |                 |
|-------------------------------------|------------------|-----------------|
| subjects affected / exposed         | 5 / 199 (2.51%)  | 9 / 199 (4.52%) |
| occurrences (all)                   | 5                | 9               |
| Angular cheilitis                   |                  |                 |
| subjects affected / exposed         | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)                   | 1                | 0               |
| Body odor                           |                  |                 |
| subjects affected / exposed         | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)                   | 0                | 1               |
| Bullous dermatitis                  |                  |                 |
| subjects affected / exposed         | 1 / 199 (0.50%)  | 1 / 199 (0.50%) |
| occurrences (all)                   | 1                | 1               |
| Cellulitis                          |                  |                 |
| subjects affected / exposed         | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)                   | 0                | 1               |
| Corner mouth subcutaneous swelling  |                  |                 |
| subjects affected / exposed         | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)                   | 1                | 0               |
| Cutaneous eruption                  |                  |                 |
| subjects affected / exposed         | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)                   | 0                | 1               |
| Cutaneous erythema                  |                  |                 |
| subjects affected / exposed         | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)                   | 1                | 0               |
| Dry skin                            |                  |                 |
| subjects affected / exposed         | 18 / 199 (9.05%) | 7 / 199 (3.52%) |
| occurrences (all)                   | 18               | 7               |
| Eczema                              |                  |                 |
| subjects affected / exposed         | 5 / 199 (2.51%)  | 2 / 199 (1.01%) |
| occurrences (all)                   | 5                | 2               |
| Erythema                            |                  |                 |
| subjects affected / exposed         | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)                   | 0                | 1               |
| Erythema multiforme                 |                  |                 |
| subjects affected / exposed         | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)                   | 1                | 0               |
| Erythromatosis finger lesion (left) |                  |                 |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Eschar                      |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Exfoliative dermatitis      |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Face cutaneous toxicity     |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Face erythema               |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 1                | 1               |
| Folliculitis                |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Hyperhidrosis               |                  |                 |
| subjects affected / exposed | 10 / 199 (5.03%) | 3 / 199 (1.51%) |
| occurrences (all)           | 10               | 3               |
| Leg skin tear               |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Lower leg red spot (right)  |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Nail changes                |                  |                 |
| subjects affected / exposed | 2 / 199 (1.01%)  | 2 / 199 (1.01%) |
| occurrences (all)           | 2                | 2               |
| Nail fingers erythema       |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Nasal mucositis             |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Neck spots                  |                  |                 |

|                                                  |                   |                   |
|--------------------------------------------------|-------------------|-------------------|
| subjects affected / exposed                      | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                | 1                 | 0                 |
| Nodular skin elbows erythema                     |                   |                   |
| subjects affected / exposed                      | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                | 1                 | 0                 |
| Non-pruginous erythematous muscle lesion (right) |                   |                   |
| subjects affected / exposed                      | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                | 1                 | 0                 |
| Pain of skin                                     |                   |                   |
| subjects affected / exposed                      | 2 / 199 (1.01%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                | 2                 | 0                 |
| Palmar-plantar erythrodysesthesia syndrome       |                   |                   |
| subjects affected / exposed                      | 0 / 199 (0.00%)   | 2 / 199 (1.01%)   |
| occurrences (all)                                | 0                 | 2                 |
| Penis erosions                                   |                   |                   |
| subjects affected / exposed                      | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                | 1                 | 0                 |
| Pharyngeal erythema                              |                   |                   |
| subjects affected / exposed                      | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                | 1                 | 0                 |
| Pityriasis versicolor                            |                   |                   |
| subjects affected / exposed                      | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                | 1                 | 0                 |
| Pruritus                                         |                   |                   |
| subjects affected / exposed                      | 35 / 199 (17.59%) | 24 / 199 (12.06%) |
| occurrences (all)                                | 35                | 24                |
| Psoriasis                                        |                   |                   |
| subjects affected / exposed                      | 2 / 199 (1.01%)   | 0 / 199 (0.00%)   |
| occurrences (all)                                | 2                 | 0                 |
| Rash                                             |                   |                   |
| subjects affected / exposed                      | 4 / 199 (2.01%)   | 4 / 199 (2.01%)   |
| occurrences (all)                                | 4                 | 4                 |
| Rash acneiform                                   |                   |                   |

|                             |                   |                  |
|-----------------------------|-------------------|------------------|
| subjects affected / exposed | 11 / 199 (5.53%)  | 6 / 199 (3.02%)  |
| occurrences (all)           | 11                | 6                |
| Rash maculo-papular         |                   |                  |
| subjects affected / exposed | 35 / 199 (17.59%) | 18 / 199 (9.05%) |
| occurrences (all)           | 35                | 18               |
| Rosacea                     |                   |                  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)  |
| occurrences (all)           | 1                 | 0                |
| Scalp pain                  |                   |                  |
| subjects affected / exposed | 2 / 199 (1.01%)   | 2 / 199 (1.01%)  |
| occurrences (all)           | 2                 | 2                |
| Scalp spots                 |                   |                  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)  |
| occurrences (all)           | 1                 | 0                |
| Scleroderma                 |                   |                  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)  |
| occurrences (all)           | 1                 | 0                |
| Shin itching                |                   |                  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)  |
| occurrences (all)           | 1                 | 0                |
| Skin atrophy                |                   |                  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)  |
| occurrences (all)           | 1                 | 0                |
| Skin hyperpigmentation      |                   |                  |
| subjects affected / exposed | 4 / 199 (2.01%)   | 1 / 199 (0.50%)  |
| occurrences (all)           | 4                 | 1                |
| Skin hypopigmentation       |                   |                  |
| subjects affected / exposed | 2 / 199 (1.01%)   | 0 / 199 (0.00%)  |
| occurrences (all)           | 2                 | 0                |
| Skin toxicity               |                   |                  |
| subjects affected / exposed | 1 / 199 (0.50%)   | 0 / 199 (0.00%)  |
| occurrences (all)           | 1                 | 0                |
| Skin ulceration             |                   |                  |
| subjects affected / exposed | 2 / 199 (1.01%)   | 0 / 199 (0.00%)  |
| occurrences (all)           | 2                 | 0                |
| Stoma site irritation       |                   |                  |

|                                                       |                 |                 |  |
|-------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                           | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                     | 1               | 0               |  |
| Urticaria                                             |                 |                 |  |
| subjects affected / exposed                           | 0 / 199 (0.00%) | 4 / 199 (2.01%) |  |
| occurrences (all)                                     | 0               | 4               |  |
| Venous eczema                                         |                 |                 |  |
| subjects affected / exposed                           | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                     | 0               | 1               |  |
| Wart lesions                                          |                 |                 |  |
| subjects affected / exposed                           | 0 / 199 (0.00%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                     | 0               | 1               |  |
| Renal and urinary disorders                           |                 |                 |  |
| Acute kidney disease                                  |                 |                 |  |
| subjects affected / exposed                           | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                     | 1               | 0               |  |
| Acute kidney injury                                   |                 |                 |  |
| subjects affected / exposed                           | 4 / 199 (2.01%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                     | 4               | 1               |  |
| Chronic kidney disease                                |                 |                 |  |
| subjects affected / exposed                           | 2 / 199 (1.01%) | 2 / 199 (1.01%) |  |
| occurrences (all)                                     | 2               | 2               |  |
| Creatinine clearance decreased                        |                 |                 |  |
| subjects affected / exposed                           | 1 / 199 (0.50%) | 1 / 199 (0.50%) |  |
| occurrences (all)                                     | 1               | 1               |  |
| Cystitis noninfective                                 |                 |                 |  |
| subjects affected / exposed                           | 2 / 199 (1.01%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                     | 2               | 0               |  |
| Dysuria                                               |                 |                 |  |
| subjects affected / exposed                           | 6 / 199 (3.02%) | 4 / 199 (2.01%) |  |
| occurrences (all)                                     | 6               | 4               |  |
| Estimated glomerular filtration rate (eGFR) decreased |                 |                 |  |
| subjects affected / exposed                           | 1 / 199 (0.50%) | 0 / 199 (0.00%) |  |
| occurrences (all)                                     | 1               | 0               |  |
| Glomerular filtration rate decreased                  |                 |                 |  |

|                              |                   |                   |
|------------------------------|-------------------|-------------------|
| subjects affected / exposed  | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 1                 | 0                 |
| Glomerulonephritis           |                   |                   |
| subjects affected / exposed  | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 1                 | 0                 |
| Hematuria                    |                   |                   |
| subjects affected / exposed  | 8 / 199 (4.02%)   | 2 / 199 (1.01%)   |
| occurrences (all)            | 8                 | 2                 |
| Nephritis                    |                   |                   |
| subjects affected / exposed  | 4 / 199 (2.01%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 4                 | 0                 |
| Nocturia                     |                   |                   |
| subjects affected / exposed  | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 1                 | 0                 |
| Proteinuria                  |                   |                   |
| subjects affected / exposed  | 33 / 199 (16.58%) | 21 / 199 (10.55%) |
| occurrences (all)            | 33                | 21                |
| Renal calculi                |                   |                   |
| subjects affected / exposed  | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)            | 0                 | 1                 |
| Renal failure                |                   |                   |
| subjects affected / exposed  | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 1                 | 0                 |
| Renal function deterioration |                   |                   |
| subjects affected / exposed  | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 1                 | 0                 |
| Renal impairment             |                   |                   |
| subjects affected / exposed  | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 1                 | 0                 |
| Renal toxicity               |                   |                   |
| subjects affected / exposed  | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 1                 | 0                 |
| Urine ketones high levels    |                   |                   |
| subjects affected / exposed  | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)            | 1                 | 0                 |
| Urethra bleeding             |                   |                   |

|                                                 |                   |                 |  |
|-------------------------------------------------|-------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%) |  |
| occurrences (all)                               | 1                 | 0               |  |
| Urethra burning                                 |                   |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%) |  |
| occurrences (all)                               | 1                 | 0               |  |
| Urinary flow change                             |                   |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%) |  |
| occurrences (all)                               | 1                 | 0               |  |
| Urinary frequency                               |                   |                 |  |
| subjects affected / exposed                     | 5 / 199 (2.51%)   | 6 / 199 (3.02%) |  |
| occurrences (all)                               | 5                 | 6               |  |
| Urinary retention                               |                   |                 |  |
| subjects affected / exposed                     | 6 / 199 (3.02%)   | 2 / 199 (1.01%) |  |
| occurrences (all)                               | 6                 | 2               |  |
| Urinary symptoms                                |                   |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%) |  |
| occurrences (all)                               | 1                 | 0               |  |
| Urine offensive smell                           |                   |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%)   | 1 / 199 (0.50%) |  |
| occurrences (all)                               | 0                 | 1               |  |
| Endocrine disorders                             |                   |                 |  |
| Diabetes (type II)                              |                   |                 |  |
| subjects affected / exposed                     | 1 / 199 (0.50%)   | 0 / 199 (0.00%) |  |
| occurrences (all)                               | 1                 | 0               |  |
| Hyperparathyroidism                             |                   |                 |  |
| subjects affected / exposed                     | 0 / 199 (0.00%)   | 1 / 199 (0.50%) |  |
| occurrences (all)                               | 0                 | 1               |  |
| Hyperthyroidism                                 |                   |                 |  |
| subjects affected / exposed                     | 13 / 199 (6.53%)  | 3 / 199 (1.51%) |  |
| occurrences (all)                               | 13                | 3               |  |
| Hypothyroidism                                  |                   |                 |  |
| subjects affected / exposed                     | 23 / 199 (11.56%) | 5 / 199 (2.51%) |  |
| occurrences (all)                               | 23                | 5               |  |
| Musculoskeletal and connective tissue disorders |                   |                 |  |

|                                       |                   |                   |
|---------------------------------------|-------------------|-------------------|
| Arthralgia                            |                   |                   |
| subjects affected / exposed           | 25 / 199 (12.56%) | 20 / 199 (10.05%) |
| occurrences (all)                     | 25                | 20                |
| Arthritis                             |                   |                   |
| subjects affected / exposed           | 5 / 199 (2.51%)   | 1 / 199 (0.50%)   |
| occurrences (all)                     | 5                 | 1                 |
| Back pain                             |                   |                   |
| subjects affected / exposed           | 24 / 199 (12.06%) | 17 / 199 (8.54%)  |
| occurrences (all)                     | 24                | 17                |
| Bone pain                             |                   |                   |
| subjects affected / exposed           | 7 / 199 (3.52%)   | 5 / 199 (2.51%)   |
| occurrences (all)                     | 7                 | 5                 |
| Bursitis                              |                   |                   |
| subjects affected / exposed           | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)                     | 0                 | 1                 |
| Calf swelling (right)                 |                   |                   |
| subjects affected / exposed           | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)                     | 0                 | 1                 |
| Chest wall pain                       |                   |                   |
| subjects affected / exposed           | 5 / 199 (2.51%)   | 13 / 199 (6.53%)  |
| occurrences (all)                     | 5                 | 13                |
| Compression inferior limb sensitivity |                   |                   |
| subjects affected / exposed           | 0 / 199 (0.00%)   | 1 / 199 (0.50%)   |
| occurrences (all)                     | 0                 | 1                 |
| Flank pain                            |                   |                   |
| subjects affected / exposed           | 10 / 199 (5.03%)  | 9 / 199 (4.52%)   |
| occurrences (all)                     | 10                | 9                 |
| Generalized muscle weakness           |                   |                   |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 3 / 199 (1.51%)   |
| occurrences (all)                     | 1                 | 3                 |
| Hemithoracic tenderness (right)       |                   |                   |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                     | 1                 | 0                 |
| Ilical pain                           |                   |                   |
| subjects affected / exposed           | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |
| occurrences (all)                     | 1                 | 0                 |

|                                               |                  |                  |
|-----------------------------------------------|------------------|------------------|
| Joint effusion                                |                  |                  |
| subjects affected / exposed                   | 1 / 199 (0.50%)  | 0 / 199 (0.00%)  |
| occurrences (all)                             | 1                | 0                |
| Joint range of motion decreased               |                  |                  |
| subjects affected / exposed                   | 2 / 199 (1.01%)  | 0 / 199 (0.00%)  |
| occurrences (all)                             | 2                | 0                |
| Maxillary/ mandibular bones alveolar<br>lysis |                  |                  |
| subjects affected / exposed                   | 0 / 199 (0.00%)  | 1 / 199 (0.50%)  |
| occurrences (all)                             | 0                | 1                |
| Muscle cramp                                  |                  |                  |
| subjects affected / exposed                   | 4 / 199 (2.01%)  | 1 / 199 (0.50%)  |
| occurrences (all)                             | 4                | 1                |
| Muscle weakness lower limb                    |                  |                  |
| subjects affected / exposed                   | 2 / 199 (1.01%)  | 0 / 199 (0.00%)  |
| occurrences (all)                             | 2                | 0                |
| Muscle weakness upper limb                    |                  |                  |
| subjects affected / exposed                   | 1 / 199 (0.50%)  | 0 / 199 (0.00%)  |
| occurrences (all)                             | 1                | 0                |
| Muscular pain                                 |                  |                  |
| subjects affected / exposed                   | 0 / 199 (0.00%)  | 1 / 199 (0.50%)  |
| occurrences (all)                             | 0                | 1                |
| Myalgia                                       |                  |                  |
| subjects affected / exposed                   | 15 / 199 (7.54%) | 2 / 199 (1.01%)  |
| occurrences (all)                             | 15               | 2                |
| Neck pain                                     |                  |                  |
| subjects affected / exposed                   | 9 / 199 (4.52%)  | 5 / 199 (2.51%)  |
| occurrences (all)                             | 9                | 5                |
| Osteoporosis                                  |                  |                  |
| subjects affected / exposed                   | 0 / 199 (0.00%)  | 1 / 199 (0.50%)  |
| occurrences (all)                             | 0                | 1                |
| Pain in extremity                             |                  |                  |
| subjects affected / exposed                   | 18 / 199 (9.05%) | 11 / 199 (5.53%) |
| occurrences (all)                             | 18               | 11               |
| Polimialgia arthralgic                        |                  |                  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%)  |  |
| occurrences (all)           | 1                | 0                |  |
| Polyalgia                   |                  |                  |  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%)  |  |
| occurrences (all)           | 1                | 0                |  |
| Rotator cuff injury         |                  |                  |  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%)  |  |
| occurrences (all)           | 1                | 0                |  |
| Sciatalgia                  |                  |                  |  |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%)  |  |
| occurrences (all)           | 0                | 1                |  |
| Shoulder pain               |                  |                  |  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 3 / 199 (1.51%)  |  |
| occurrences (all)           | 1                | 3                |  |
| Shoulder pain (right)       |                  |                  |  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 1 / 199 (0.50%)  |  |
| occurrences (all)           | 1                | 1                |  |
| Tendonitis                  |                  |                  |  |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%)  |  |
| occurrences (all)           | 0                | 1                |  |
| Infections and infestations |                  |                  |  |
| Bladder infection           |                  |                  |  |
| subjects affected / exposed | 2 / 199 (1.01%)  | 0 / 199 (0.00%)  |  |
| occurrences (all)           | 2                | 0                |  |
| Bronchial infection         |                  |                  |  |
| subjects affected / exposed | 4 / 199 (2.01%)  | 4 / 199 (2.01%)  |  |
| occurrences (all)           | 4                | 4                |  |
| COVID-19 infection          |                  |                  |  |
| subjects affected / exposed | 17 / 199 (8.54%) | 10 / 199 (5.03%) |  |
| occurrences (all)           | 17               | 10               |  |
| Candidiasis                 |                  |                  |  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%)  |  |
| occurrences (all)           | 1                | 0                |  |
| Catheter related infection  |                  |                  |  |
| subjects affected / exposed | 0 / 199 (0.00%)  | 2 / 199 (1.01%)  |  |
| occurrences (all)           | 0                | 2                |  |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| Cold                        |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Conjunctivitis              |                  |                 |
| subjects affected / exposed | 13 / 199 (6.53%) | 6 / 199 (3.02%) |
| occurrences (all)           | 13               | 6               |
| Dental abscess              |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Dental phlegmon             |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Device related infection    |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Dorsal boil                 |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Enterocolitis infectious    |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 0                | 1               |
| Esophageal infection        |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 1                | 1               |
| Eye infection               |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 1                | 1               |
| Fungemia                    |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 1 / 199 (0.50%) |
| occurrences (all)           | 1                | 1               |
| Gastroenteritis             |                  |                 |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Gum infection               |                  |                 |
| subjects affected / exposed | 0 / 199 (0.00%)  | 4 / 199 (2.01%) |
| occurrences (all)           | 0                | 4               |

|                                                                                 |                      |                        |
|---------------------------------------------------------------------------------|----------------------|------------------------|
| Herpes simplex reactivation<br>subjects affected / exposed<br>occurrences (all) | 4 / 199 (2.01%)<br>4 | 1 / 199 (0.50%)<br>1   |
| Infected big toe (right)<br>subjects affected / exposed<br>occurrences (all)    | 0 / 199 (0.00%)<br>0 | 1 / 199 (0.50%)<br>1   |
| Infection (unknown source)<br>subjects affected / exposed<br>occurrences (all)  | 3 / 199 (1.51%)<br>3 | 0 / 199 (0.00%)<br>0   |
| Kidney infection<br>subjects affected / exposed<br>occurrences (all)            | 1 / 199 (0.50%)<br>1 | 0 / 199 (0.00%)<br>0   |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 199 (0.50%)<br>1 | 0 / 199 (0.00%)<br>0   |
| Lip infection<br>subjects affected / exposed<br>occurrences (all)               | 1 / 199 (0.50%)<br>1 | 0 / 199 (0.00%)<br>0   |
| Lung infection<br>subjects affected / exposed<br>occurrences (all)              | 6 / 199 (3.02%)<br>6 | 13 / 199 (6.53%)<br>13 |
| Lymph gland infection<br>subjects affected / exposed<br>occurrences (all)       | 1 / 199 (0.50%)<br>1 | 0 / 199 (0.00%)<br>0   |
| Mouth abcess<br>subjects affected / exposed<br>occurrences (all)                | 0 / 199 (0.00%)<br>0 | 1 / 199 (0.50%)<br>1   |
| Mucosal infection<br>subjects affected / exposed<br>occurrences (all)           | 4 / 199 (2.01%)<br>4 | 4 / 199 (2.01%)<br>4   |
| Nail infection<br>subjects affected / exposed<br>occurrences (all)              | 1 / 199 (0.50%)<br>1 | 1 / 199 (0.50%)<br>1   |
| Otitis media<br>subjects affected / exposed<br>occurrences (all)                | 0 / 199 (0.00%)<br>0 | 1 / 199 (0.50%)<br>1   |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| Papulopustular rash         |                 |                 |
| subjects affected / exposed | 3 / 199 (1.51%) | 0 / 199 (0.00%) |
| occurrences (all)           | 3               | 0               |
| Penile infection            |                 |                 |
| subjects affected / exposed | 3 / 199 (1.51%) | 1 / 199 (0.50%) |
| occurrences (all)           | 3               | 1               |
| Pleural infection           |                 |                 |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Port infection              |                 |                 |
| subjects affected / exposed | 1 / 199 (0.50%) | 1 / 199 (0.50%) |
| occurrences (all)           | 1               | 1               |
| Prostate infection          |                 |                 |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 199 (0.50%) |
| occurrences (all)           | 0               | 1               |
| Pyrexia                     |                 |                 |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 199 (0.50%) |
| occurrences (all)           | 0               | 1               |
| Rash pustular               |                 |                 |
| subjects affected / exposed | 2 / 199 (1.01%) | 1 / 199 (0.50%) |
| occurrences (all)           | 2               | 1               |
| Rhinitis infective          |                 |                 |
| subjects affected / exposed | 2 / 199 (1.01%) | 2 / 199 (1.01%) |
| occurrences (all)           | 2               | 2               |
| Sepsis                      |                 |                 |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Shingles                    |                 |                 |
| subjects affected / exposed | 3 / 199 (1.51%) | 2 / 199 (1.01%) |
| occurrences (all)           | 3               | 2               |
| Sialoadenitis               |                 |                 |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 199 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Sinusitis                   |                 |                 |
| subjects affected / exposed | 2 / 199 (1.01%) | 3 / 199 (1.51%) |
| occurrences (all)           | 2               | 3               |

|                                    |                   |                   |  |
|------------------------------------|-------------------|-------------------|--|
| Skin infection                     |                   |                   |  |
| subjects affected / exposed        | 8 / 199 (4.02%)   | 6 / 199 (3.02%)   |  |
| occurrences (all)                  | 8                 | 6                 |  |
| Soft tissue infection              |                   |                   |  |
| subjects affected / exposed        | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                  | 1                 | 0                 |  |
| Staphylococcus Aureus infection    |                   |                   |  |
| subjects affected / exposed        | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                  | 1                 | 0                 |  |
| Thrush                             |                   |                   |  |
| subjects affected / exposed        | 8 / 199 (4.02%)   | 7 / 199 (3.52%)   |  |
| occurrences (all)                  | 8                 | 7                 |  |
| Tonsillitis                        |                   |                   |  |
| subjects affected / exposed        | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                  | 1                 | 0                 |  |
| Tooth infection                    |                   |                   |  |
| subjects affected / exposed        | 8 / 199 (4.02%)   | 6 / 199 (3.02%)   |  |
| occurrences (all)                  | 8                 | 6                 |  |
| Upper respiratory infection        |                   |                   |  |
| subjects affected / exposed        | 9 / 199 (4.52%)   | 7 / 199 (3.52%)   |  |
| occurrences (all)                  | 9                 | 7                 |  |
| Urinary tract infection            |                   |                   |  |
| subjects affected / exposed        | 19 / 199 (9.55%)  | 8 / 199 (4.02%)   |  |
| occurrences (all)                  | 19                | 8                 |  |
| Wound infection                    |                   |                   |  |
| subjects affected / exposed        | 2 / 199 (1.01%)   | 2 / 199 (1.01%)   |  |
| occurrences (all)                  | 2                 | 2                 |  |
| Metabolism and nutrition disorders |                   |                   |  |
| Anorexia                           |                   |                   |  |
| subjects affected / exposed        | 58 / 199 (29.15%) | 54 / 199 (27.14%) |  |
| occurrences (all)                  | 58                | 54                |  |
| Dehydration                        |                   |                   |  |
| subjects affected / exposed        | 1 / 199 (0.50%)   | 0 / 199 (0.00%)   |  |
| occurrences (all)                  | 1                 | 0                 |  |
| Hypercalcemia                      |                   |                   |  |

|                             |                  |                  |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 13 / 199 (6.53%) | 11 / 199 (5.53%) |
| occurrences (all)           | 13               | 11               |
| Hyperglycemia               |                  |                  |
| subjects affected / exposed | 13 / 199 (6.53%) | 11 / 199 (5.53%) |
| occurrences (all)           | 13               | 11               |
| Hyperkalemia                |                  |                  |
| subjects affected / exposed | 4 / 199 (2.01%)  | 4 / 199 (2.01%)  |
| occurrences (all)           | 4                | 4                |
| Hyperlipidemia              |                  |                  |
| subjects affected / exposed | 0 / 199 (0.00%)  | 1 / 199 (0.50%)  |
| occurrences (all)           | 0                | 1                |
| Hypermagnesemia             |                  |                  |
| subjects affected / exposed | 2 / 199 (1.01%)  | 2 / 199 (1.01%)  |
| occurrences (all)           | 2                | 2                |
| Hypernatremia               |                  |                  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%)  |
| occurrences (all)           | 1                | 0                |
| Hyperphosphatemia           |                  |                  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 1 / 199 (0.50%)  |
| occurrences (all)           | 1                | 1                |
| Hypertriglyceridemia        |                  |                  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 1 / 199 (0.50%)  |
| occurrences (all)           | 1                | 1                |
| Hyperuricemia               |                  |                  |
| subjects affected / exposed | 8 / 199 (4.02%)  | 4 / 199 (2.01%)  |
| occurrences (all)           | 8                | 4                |
| Hypoalbuminemia             |                  |                  |
| subjects affected / exposed | 6 / 199 (3.02%)  | 4 / 199 (2.01%)  |
| occurrences (all)           | 6                | 4                |
| Hypocalcemia                |                  |                  |
| subjects affected / exposed | 6 / 199 (3.02%)  | 1 / 199 (0.50%)  |
| occurrences (all)           | 6                | 1                |
| Hypokalemia                 |                  |                  |
| subjects affected / exposed | 8 / 199 (4.02%)  | 6 / 199 (3.02%)  |
| occurrences (all)           | 8                | 6                |
| Hypomagnesemia              |                  |                  |

|                             |                  |                   |  |
|-----------------------------|------------------|-------------------|--|
| subjects affected / exposed | 18 / 199 (9.05%) | 27 / 199 (13.57%) |  |
| occurrences (all)           | 18               | 27                |  |
| Hyponatremia                |                  |                   |  |
| subjects affected / exposed | 9 / 199 (4.52%)  | 2 / 199 (1.01%)   |  |
| occurrences (all)           | 9                | 2                 |  |
| Hypophosphatemia            |                  |                   |  |
| subjects affected / exposed | 2 / 199 (1.01%)  | 1 / 199 (0.50%)   |  |
| occurrences (all)           | 2                | 1                 |  |
| Hypoproteinemia             |                  |                   |  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%)   |  |
| occurrences (all)           | 1                | 0                 |  |
| Zinc deficiency             |                  |                   |  |
| subjects affected / exposed | 1 / 199 (0.50%)  | 0 / 199 (0.00%)   |  |
| occurrences (all)           | 1                | 0                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 08 December 2020 | <p>The protocol has been updated to account for the new safety information for atezolizumab, including the addition of the newly identified risks of immune-mediated myositis and immune-mediated nephritis. The Management of atezolizumab related toxicities has been updated based on the latest version of the atezolizumab IB Version 15, July 2019, the Addendum 2, December 2019 to the IB V15 and the diagnostic criteria and management guidelines for haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) replacing systemic immune activation (SIS) communicated by Roche separately through a Safety Memo.</p> <p>In addition, the list of AESIs have been updated to reflect the new safety information and active autoimmune disease that required systemic treatment in the past 2 year as well as history of active diverticulitis have been added as exclusion criteria.</p> <p>Furthermore, some minor protocol clarifications have been added and some ambiguities and typos eliminated.</p> |
| 10 May 2021      | <p>The protocol is being amended to change the primary endpoint from a co-primary endpoint of overall survival (OS) and progression free survival (PFS) to overall survival only. This change is associated with an increase in sample size to a total of 400 randomized patients.</p> <p>Several adaptations were made throughout the protocol to account for the change to OS as primary endpoint, the resulting samples size increase and the adaptation of the trial duration.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 03 May 2024      | <p>The protocol is being amended to include the option for the treatment beyond trial closure through the F. Hoffmann-La Roche Ltd. Post-Trial Access Programme (PTAP). The description of this PTAP option has been added as a separate subsection to Section 9.</p> <p>In addition, several formatting changes were made throughout the protocol to account for the change in the sponsor name, as notified earlier.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported