



## Clinical trial results:

**A phase II, randomized, active-controlled, multicenter study comparing the efficacy and safety of targeted therapy or cancer immunotherapy guided by genomic profiling versus platinum-based chemotherapy in patients with cancer of unknown primary site who have received three cycles of platinum doublet chemotherapy**

### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2017-003040-20   |
| Trial protocol           | GB AT EE IE DE CZ FI LV HU PL FR ES BG PT HR NO NL DK CY |
| Global end of trial date | IT RO  |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v3 (current)     |
| This version publication date  | 23 November 2025 |
| First version publication date | 06 March 2024    |

|                         |  |
|-------------------------|--|
| Version creation reason |  |
|-------------------------|--|

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MX39795 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03498521 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Hoffmann-La Roche   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, 4070   |
| Public contact               | F. Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Interim          |
| Date of interim/final analysis                       | 14 February 2023 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 14 February 2023 |
| Global end of trial reached?                         | No               |

Notes:

## General information about the trial

Main objective of the trial:

Study MX39795 compared the efficacy and safety of molecularly-guided therapy versus standard platinum-containing chemotherapy in patients with poor prognosis cancer of unknown primary site (CUP; non-specific subset) who have achieved disease control (CR, PR or SD) after 3 cycles of first-line platinum-based induction chemotherapy. Molecularly-guided therapies included 10 targeted cancer therapy regimens and 2 cancer immunotherapy regimens and were chosen based on each participant's comprehensive genomic profile.

Protection of trial subjects:

All participants were required to sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 12 April 2018 |
| 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 | Australia: 24      |
| Country: Number of subjects enrolled | Austria: 3         |
| Country: Number of subjects enrolled | Bulgaria: 3        |
| Country: Number of subjects enrolled | Brazil: 29         |
| Country: Number of subjects enrolled | Switzerland: 4     |
| Country: Number of subjects enrolled | Chile: 8           |
| Country: Number of subjects enrolled | Colombia: 6        |
| Country: Number of subjects enrolled | Czechia: 17        |
| Country: Number of subjects enrolled | Germany: 65        |
| Country: Number of subjects enrolled | Denmark: 4         |
| Country: Number of subjects enrolled | Spain: 54          |
| Country: Number of subjects enrolled | Estonia: 3         |
| Country: Number of subjects enrolled | Finland: 6         |
| Country: Number of subjects enrolled | France: 50         |
| Country: Number of subjects enrolled | United Kingdom: 60 |
| Country: Number of subjects enrolled | Greece: 15         |
| Country: Number of subjects enrolled | Croatia: 2         |
| Country: Number of subjects enrolled | Hungary: 4         |
| Country: Number of subjects enrolled | Ireland: 7         |
| Country: Number of subjects enrolled | Israel: 11         |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Italy: 22              |
| Country: Number of subjects enrolled | Japan: 13              |
| Country: Number of subjects enrolled | Korea, Republic of: 22 |
| Country: Number of subjects enrolled | Latvia: 6              |
| Country: Number of subjects enrolled | Mexico: 6              |
| Country: Number of subjects enrolled | Netherlands: 12        |
| Country: Number of subjects enrolled | Norway: 5              |
| Country: Number of subjects enrolled | Peru: 2                |
| Country: Number of subjects enrolled | Poland: 1              |
| Country: Number of subjects enrolled | Portugal: 4            |
| Country: Number of subjects enrolled | Romania: 12            |
| Country: Number of subjects enrolled | Thailand: 8            |
| Country: Number of subjects enrolled | Türkiye: 41            |
| Worldwide total number of subjects   | 529                    |
| EEA total number of subjects         | 295                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 309 |
| From 65 to 84 years                       | 220 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Eligible participants included adults with poor prognosis cancer of unknown primary site (CUP).

### 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>             | Molecularly-Guided Therapy (MGT) Category 1 |

Arm description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). MGT was chosen based on each participant's comprehensive genomic profile and administered until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Entrectinib   |
| Investigational medicinal product code |               |
| Other name                             | RO7102122     |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Administered as recommended in its US label for patients with NTRK gene fusions or ROS1 gene rearrangements (600 mg QD) until loss of clinical benefit or unacceptable toxicity.

|  |           |
|--|-----------|
| Investigational medicinal product name | Alectinib |
| Investigational medicinal product code |           |
| Other name                             | RO5424802 |
| Pharmaceutical forms                   | Capsule   |
| Routes of administration               | Oral use  |

Dosage and administration details:

Administered as recommended for ALK-positive non-small cell lung cancer (NSCLC) (600 mg twice daily (BID) until loss of clinical benefit or unacceptable toxicity.

|  |           |
|--|-----------|
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code |           |
| Other name                             | RO508231  |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Administered as recommended in its EMA Summary of Product Characteristics (EU SmPC) for advanced NSCLC (150 mg per day (QD)) in combination with bevacizumab until loss of clinical benefit or unacceptable toxicity.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Atezolizumab          |
| Investigational medicinal product code |                       |
| Other name                             | RO5541267             |
| Pharmaceutical forms                   | Solution for infusion |

|   |                             |
|---|-----------------------------|
| Routes of administration  | Intravenous use             |
| Dosage and administration details:  |                             |
| Administered alone or in combination with platinum-based chemotherapy as recommended for urinary carcinoma or NSCLC (1200 mg IV infusion over 60 min every three weeks (Q3W)) until loss of clinical benefit or unacceptable toxicity.                            |                             |
| Investigational medicinal product name  | Vismodegib                  |
| Investigational medicinal product code  |                             |
| Other name  | RO5450815                   |
| Pharmaceutical forms  | Capsule                     |
| Routes of administration  | Oral use                    |
| Dosage and administration details:  |                             |
| Administered as recommended for metastatic basal cell carcinoma (150 mg QD) until loss of clinical benefit or toxicity.   |                             |
| Investigational medicinal product name  | Pemigatinib                 |
| Investigational medicinal product code  |                             |
| Other name  | RO7496200                   |
| Pharmaceutical forms  | Tablet                      |
| Routes of administration  | Oral use                    |
| Dosage and administration details:  |                             |
| Administered as recommended for advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other rearrangements (13.5 mg QD) across a 21-day treatment cycle until loss of clinical benefit or unacceptable toxicity.  |                             |
| Investigational medicinal product name  | Olaparib                    |
| Investigational medicinal product code  |                             |
| Other name  | RO5508245                   |
| Pharmaceutical forms  | Capsule, Film-coated tablet |
| Routes of administration  | Oral use                    |
| Dosage and administration details:  |                             |
| Administered as recommended for patients with germline BRCA-mutated advanced ovarian cancer (400 mg twice-daily (BID) for capsules, or 300 mg BID for film-coated tablets) until loss of clinical benefit or unacceptable toxicity.                               |                             |
| Investigational medicinal product name  | Ivosidenib                  |
| Investigational medicinal product code  |                             |
| Other name  | RO7499824                   |
| Pharmaceutical forms  | Tablet                      |
| Routes of administration  | Oral use                    |
| Dosage and administration details:  |                             |
| Administered as recommended in its US label for patients with newly-diagnosed or relapsed/refractory acute myeloid leukemia with a susceptible IDH1 mutation (500 mg QD across a 28-day treatment cycle) until loss of clinical benefit or unacceptable toxicity. |                             |
| Investigational medicinal product name  | Paclitaxel                  |
| Investigational medicinal product code  |                             |
| Other name  | RO0247506                   |
| Pharmaceutical forms  | Solution for infusion       |
| Routes of administration  | Intravenous use             |
| Dosage and administration details:  |                             |
| Administered at a dose of 175 mg/m <sup>2</sup> on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.   |                             |
| Investigational medicinal product name  | Cisplatin                   |
| Investigational medicinal product code  |                             |
| Other name  | RO0232538                   |
| Pharmaceutical forms  | Solution for infusion       |
| Routes of administration  | Intravenous use             |

Dosage and administration details:

Administered at a dose of 60-75 mg/m<sup>2</sup> on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |   |
|--|---|
| Investigational medicinal product name | Carboplatin                                   |
| Investigational medicinal product code |   |
| Other name                             | RO4843791                                     |
| Pharmaceutical forms                   | Solution for injection, Solution for infusion |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

Administered weekly as part of platinum-based chemotherapy at induction (3 cycles) at an AUC dose calculated by the Calvert formula for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Pertuzumab            |
| Investigational medicinal product code |                       |
| Other name                             | RO4368451             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered as recommended for advanced breast cancer with HER2 alterations (initial loading dose of 840 mg; thereafter 420 mg Q3W) in combination with trastuzumab and platinum-based chemotherapy.

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Trastuzumab            |
| Investigational medicinal product code |                        |
| Other name                             | RO0452317              |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Administered as recommended for advanced breast cancer with HER2 alterations (600 mg fixed-dose SC injection Q3W) in combination with pertuzumab and platinum-based chemotherapy.

|  |             |
|--|-------------|
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code |             |
| Other name                             | RO5514041   |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

Administered as recommended in its investigator's brochure for advanced melanoma (60 mg QD for the first 21 days of a 28-Day treatment cycle) in combination with vemurafenib until loss of clinical benefit or unacceptable toxicity.

|  |  |
|--|--|
| Investigational medicinal product name | Vemurafenib  |
| Investigational medicinal product code |  |
| Other name                             | RO5185426  |
| Pharmaceutical forms                   | Film-coated tablet and gastro-resistant granules in sachet, Film-coated tablet |
| Routes of administration               | Oral use   |

Dosage and administration details:

Administered as recommended in its investigator's brochure for advanced melanoma (960 mg BID) in combination with cobimetinib until loss of clinical benefit or unacceptable toxicity.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             | RO0247506             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 80 mg/m<sup>2</sup> on Days 1, 8, and 15 of a 28-Day cycle for 3 cycles in combination with ipatasertib.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Gemcitabine           |
| Investigational medicinal product code |                       |
| Other name                             | RO0249587             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 1000 mg/m<sup>2</sup> on Day 1 and Day 8 of a 3-week cycle as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Bevacizumab           |
| Investigational medicinal product code |                       |
| Other name                             | RO4876646             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered as recommended in its EU SmPC for advanced NSCLC (15 mg/kg Q3W) in combination with erlotinib until loss of clinical benefit or unacceptable toxicity.

|  |             |
|--|-------------|
| Investigational medicinal product name | Ipatasertib |
| Investigational medicinal product code |             |
| Other name                             | RO5532961   |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

Administered at a dose of 400 mg QD on Days 1-21 of a 28-day cycle, first in combination with paclitaxel (3 cycles) and then as monotherapy until loss of clinical benefit or unacceptable toxicity.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Chemotherapy Category 1 |
|------------------|-------------------------|

Arm description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). Participants in this arm continued to receive the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

|  |   |
|--|---|
| Arm type                               | Control                                       |
| Investigational medicinal product name | Carboplatin                                   |
| Investigational medicinal product code |   |
| Other name                             | RO4843791                                     |
| Pharmaceutical forms                   | Solution for injection, Solution for infusion |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

Administered weekly as part of platinum-based chemotherapy at induction (3 cycles) at an AUC dose calculated by the Calvert formula for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Gemcitabine           |
| Investigational medicinal product code |                       |
| Other name                             | RO0249587             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 1000 mg/m<sup>2</sup> on Day 1 and Day 8 of a 3-week cycle as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Cisplatin             |
| Investigational medicinal product code |                       |
| Other name                             | RO0232538             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 60-75 mg/m<sup>2</sup> on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             | RO0247506             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 175 mg/m<sup>2</sup> on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Category 2 |
|------------------|------------|

Arm description:

Category 2 included participants with progressive disease (PD) after 3 cycles of platinum induction chemotherapy. Participants in this arm received either MGT based on their comprehensive genomic profile until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first, or the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             | RO0247506             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 175 mg/m<sup>2</sup> on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |   |
|--|---|
| Investigational medicinal product name | Carboplatin                                   |
| Investigational medicinal product code |   |
| Other name                             | RO4843791                                     |
| Pharmaceutical forms                   | Solution for injection, Solution for infusion |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

Administered weekly as part of platinum-based chemotherapy at induction (3 cycles) at an AUC dose calculated by the Calvert formula for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |           |
|--|-----------|
| Investigational medicinal product name | Alectinib |
| Investigational medicinal product code |           |
| Other name                             | RO5424802 |
| Pharmaceutical forms                   | Capsule   |
| Routes of administration               | Oral use  |

Dosage and administration details:

Administered as recommended for ALK-positive non-small cell lung cancer (NSCLC) (600 mg twice daily (BID) until loss of clinical benefit or unacceptable toxicity.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Gemcitabine           |
| Investigational medicinal product code |                       |
| Other name                             | RO0249587             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 1000 mg/m<sup>2</sup> on Day 1 and Day 8 of a 3-week cycle as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.



|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Cisplatin             |
| Investigational medicinal product code |                       |
| Other name                             | RO0232538             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 60-75 mg/m<sup>2</sup> on Day 1 as part of platinum-based chemotherapy at induction (3 cycles) for all participants, then for a minimum of an additional 3 cycles for selected participants.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Pertuzumab            |
| Investigational medicinal product code |                       |
| Other name                             | RO4368451             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered as recommended for advanced breast cancer with HER2 alterations (initial loading dose of 840 mg; thereafter 420 mg Q3W) in combination with trastuzumab and platinum-based chemotherapy.

|  |               |
|--|---------------|
| Investigational medicinal product name | Entrectinib   |
| Investigational medicinal product code |               |
| Other name                             | RO7102122     |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Administered as recommended in its US label for patients with NTRK gene fusions or ROS1 gene rearrangements (600 mg QD) until loss of clinical benefit or unacceptable toxicity.

|  |            |
|--|------------|
| Investigational medicinal product name | Ivosidenib |
| Investigational medicinal product code |            |
| Other name                             | RO7499824  |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

Administered as recommended in its US label for patients with newly-diagnosed or relapsed/refractory acute myeloid leukemia with a susceptible IDH1 mutation (500 mg QD across a 28-day treatment cycle) until loss of clinical benefit or unacceptable toxicity.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | Olaparib                    |
| Investigational medicinal product code |                             |
| Other name                             | RO5508245                   |
| Pharmaceutical forms                   | Capsule, Film-coated tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

Administered as recommended for patients with germline BRCA-mutated advanced ovarian cancer (400 mg twice-daily (BID) for capsules, or 300 mg BID for film-coated tablets) until loss of clinical benefit or unacceptable toxicity.

|  |             |
|--|-------------|
| Investigational medicinal product name | Pemigatinib |
| Investigational medicinal product code |             |
| Other name                             | RO7496200   |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

Administered as recommended for advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other rearrangements (13.5 mg QD) across a 21-day treatment cycle until loss of clinical benefit or unacceptable toxicity.

|  |            |
|--|------------|
| Investigational medicinal product name | Vismodegib |
| Investigational medicinal product code |            |
| Other name                             | RO5450815  |

|  |  |
|--|--|
| Pharmaceutical forms   | Capsule  |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| Administered as recommended for metastatic basal cell carcinoma (150 mg QD) until loss of clinical benefit or toxicity.  |  |
| Investigational medicinal product name   | Atezolizumab   |
| Investigational medicinal product code   |  |
| Other name   | RO5541267  |
| Pharmaceutical forms   | Solution for infusion  |
| Routes of administration   | Intravenous use  |
| Dosage and administration details:   |  |
| Administered alone or in combination with platinum-based chemotherapy as recommended for urinary carcinoma or NSCLC (1200 mg IV infusion over 60 min every three weeks (Q3W)) until loss of clinical benefit or unacceptable toxicity. |  |
| Investigational medicinal product name   | Erlotinib  |
| Investigational medicinal product code   |  |
| Other name   | RO508231   |
| Pharmaceutical forms   | Tablet   |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| Administered as recommended in its EMA Summary of Product Characteristics (EU SmPC) for advanced NSCLC (150 mg per day (QD)) in combination with bevacizumab until loss of clinical benefit or unacceptable toxicity.                  |  |
| Investigational medicinal product name   | Trastuzumab  |
| Investigational medicinal product code   |  |
| Other name   | RO0452317  |
| Pharmaceutical forms   | Solution for injection   |
| Routes of administration   | Subcutaneous use   |
| Dosage and administration details:   |  |
| Administered as recommended for advanced breast cancer with HER2 alterations (600 mg fixed-dose SC injection Q3W) in combination with pertuzumab and platinum-based chemotherapy.  |  |
| Investigational medicinal product name   | Cobimetinib  |
| Investigational medicinal product code   |  |
| Other name   | RO5514041  |
| Pharmaceutical forms   | Tablet   |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| Administered as recommended in its investigator's brochure for advanced melanoma (60 mg QD for the first 21 days of a 28-Day treatment cycle) in combination with vemurafenib until loss of clinical benefit or unacceptable toxicity. |  |
| Investigational medicinal product name   | Vemurafenib  |
| Investigational medicinal product code   |  |
| Other name   | RO5185426  |
| Pharmaceutical forms   | Film-coated tablet and gastro-resistant granules in sachet, Film-coated tablet |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| Administered as recommended in its investigator's brochure for advanced melanoma (960 mg BID) in combination with cobimetinib until loss of clinical benefit or unacceptable toxicity.   |  |
| Investigational medicinal product name   | Bevacizumab  |
| Investigational medicinal product code   |  |
| Other name   | RO4876646  |
| Pharmaceutical forms   | Solution for infusion  |
| Routes of administration   | Intravenous use  |

Dosage and administration details:

Administered as recommended in its EU SmPC for advanced NSCLC (15 mg/kg Q3W) in combination with erlotinib until loss of clinical benefit or unacceptable toxicity.

|  |             |
|--|-------------|
| Investigational medicinal product name | Ipatasertib |
| Investigational medicinal product code |             |
| Other name                             | RO5532961   |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

Administered at a dose of 400 mg QD on Days 1-21 of a 28-day cycle, first in combination with paclitaxel (3 cycles) and then as monotherapy until loss of clinical benefit or unacceptable toxicity.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             | RO0247506             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered at a dose of 80 mg/m<sup>2</sup> on Days 1, 8, and 15 of a 28-Day cycle for 3 cycles in combination with ipatasertib.

| Number of subjects in period 1      | Molecularly-Guided Therapy MGT) Category 1 | Chemotherapy Category 1 | Category 2 |
|-------------------------------------|--|-------------------------|------------|
|                                     |  |                         |            |
| Started                             | 326  | 110                     | 93         |
| Completed                           | 0  | 0                       | 0          |
| Not completed                       | 326  | 110                     | 93         |
| No profile due to technical failure | 1  | -                       | -          |
| Physician decision                  | 3  | 1                       | -          |
| Consent withdrawn by subject        | 11   | 6                       | 2          |
| Death                               | 227  | 79                      | 84         |
| Study terminated by sponsor         | 79   | 21                      | 4          |
| Lost to follow-up                   | 4  | 3                       | 3          |
| Exclusion criteria                  | 1  | -                       | -          |

## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Molecularly-Guided Therapy MGT) Category 1 |
|-----------------------|--|

Reporting group description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). MGT was chosen based on each participant's comprehensive genomic profile and administered until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Chemotherapy Category 1 |
|-----------------------|-------------------------|

Reporting group description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). Participants in this arm continued to receive the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

|                       |            |
|-----------------------|------------|
| Reporting group title | Category 2 |
|-----------------------|------------|

Reporting group description:

Category 2 included participants with progressive disease (PD) after 3 cycles of platinum induction chemotherapy. Participants in this arm received either MGT based on their comprehensive genomic profile until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first, or the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

| Reporting group values                   | Molecularly-Guided Therapy MGT) Category 1 | Chemotherapy Category 1 | Category 2 |
|--|--|-------------------------|------------|
| Number of subjects                       | 326  | 110                     | 93         |
| Age categorical<br>Units: Subjects       |  |                         |            |
| Adults (18-64 years)                     | 188  | 61                      | 60         |
| From 65-84 years                         | 138  | 49                      | 33         |
| Age Continuous<br>Units: Years           |  |                         |            |
| arithmetic mean                          | 60.5                                       | 61.1                    | 59.2       |
| standard deviation                       | ± 11.5                                     | ± 11.3                  | ± 12.7     |
| Sex: Female, Male<br>Units: Participants |  |                         |            |
| Female                                   | 161  | 53                      | 44         |
| Male                                     | 165  | 57                      | 49         |
| Race, Customized<br>Units: Subjects      |  |                         |            |
| American Indian or Alaska Native         | 4  | 3                       | 1          |
| Asian                                    | 31   | 12                      | 7          |
| Black or African American                | 5  | 0                       | 0          |
| Unknown                                  | 43   | 14                      | 15         |
| White                                    | 242  | 81                      | 70         |
| Missing                                  | 1  | 0                       | 0          |
| Ethnicity, Customized<br>Units: Subjects |  |                         |            |
| Hispanic or Latino                       | 22   | 9                       | 4          |
| Not Hispanic or Latino                   | 252  | 85                      | 76         |
| Not Stated                               | 31   | 11                      | 7          |

|         |    |   |   |
|---------|----|---|---|
| Unknown | 21 | 5 | 6 |
|---------|----|---|---|

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>   | Total |  |  |
| Number of subjects  | 529   |  |  |
| Age categorical<br>Units: Subjects                                      |       |  |  |
| Adults (18-64 years)  | 309   |  |  |
| From 65-84 years  | 220   |  |  |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | -     |  |  |
| Sex: Female, Male<br>Units: Participants                                |       |  |  |
| Female  | 258   |  |  |
| Male  | 271   |  |  |
| Race, Customized<br>Units: Subjects                                     |       |  |  |
| American Indian or Alaska Native  | 8     |  |  |
| Asian   | 50    |  |  |
| Black or African American   | 5     |  |  |
| Unknown   | 72    |  |  |
| White   | 393   |  |  |
| Missing   | 1     |  |  |
| Ethnicity, Customized<br>Units: Subjects                                |       |  |  |
| Hispanic or Latino  | 35    |  |  |
| Not Hispanic or Latino  | 413   |  |  |
| Not Stated  | 49    |  |  |
| Unknown   | 32    |  |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Molecularly-Guided Therapy (MGT) Category 1 |
| Reporting group description:<br>Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). MGT was chosen based on each participant's comprehensive genomic profile and administered until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first. |   |
| Reporting group title   | Chemotherapy Category 1                     |
| Reporting group description:<br>Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). Participants in this arm continued to receive the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.   |   |
| Reporting group title   | Category 2                                  |
| Reporting group description:<br>Category 2 included participants with progressive disease (PD) after 3 cycles of platinum induction chemotherapy. Participants in this arm received either MGT based on their comprehensive genomic profile until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first, or the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.                                      |   |

### Primary: Progression Free Survival (PFS) as Assessed by the Investigator According to Response Evaluation Criteria In Solid Tumors v1.1 (RECIST v1.1)

|   |   |
|---|---|
| End point title   | Progression Free Survival (PFS) as Assessed by the Investigator According to Response Evaluation Criteria In Solid Tumors v1.1 (RECIST v1.1) <sup>[1]</sup> |
| End point description:<br>This efficacy objective was to evaluate the efficacy of MGT vs platinum chemotherapy in term of PFS in participants with CUP whose best response to 3 cycles of platinum induction chemotherapy was assessed CR, PR, or SD.   |   |
| End point type  | Primary   |
| End point timeframe:<br>From randomization to the first occurrence of disease progression or death from any cause, until 330 PFS events were observed (approx. 4.3 years for MGT Cat 1 and 3.4 years for Chemotherapy Cat 1).   |   |
| Notes:<br>[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: Endpoints for Category 2 were exploratory and were not included in this analysis. |   |

| End point values                 | Molecularly-Guided Therapy (MGT) Category 1 | Chemotherapy Category 1 |  |  |
|----------------------------------|---|-------------------------|--|--|
| Subject group type               | Reporting group                             | Reporting group         |  |  |
| Number of subjects analysed      | 326   | 110                     |  |  |
| Units: Months                    |   |                         |  |  |
| median (confidence interval 95%) | 6.14 (4.70 to 6.47)                         | 4.40 (4.17 to 6.37)     |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | PFS ITT Category 1   |
| Comparison groups                       | Molecularly-Guided Therapy MGT) Category 1 v Chemotherapy Category 1 |
| Number of subjects included in analysis | 436  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.0177   |
| Method                                  | Stratified log-rank  |
| Parameter estimate                      | Stratified Cox proportional hazard                                   |
| Point estimate                          | 0.75   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.59   |
| upper limit                             | 0.95   |

## Secondary: Overall Survival (OS)

|   |                                      |
|---|--------------------------------------|
| End point title   | Overall Survival (OS) <sup>[2]</sup> |
| End point description:<br>The intent-to-treat (ITT) population included all Category 1 randomized participants, whether or not the assigned study treatment was received. Endpoints for Category 2 were exploratory and were not included in this analysis.   |                                      |
| End point type  | Secondary                            |
| End point timeframe:<br>From randomization to death from any cause, through the end of study (approximately 4 years)  |                                      |
| Notes:<br>[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: Endpoints for Category 2 were exploratory and were not included in this analysis. |                                      |

| End point values                 | Molecularly-Guided Therapy MGT) Category 1 | Chemotherapy Category 1 |  |  |
|----------------------------------|--|-------------------------|--|--|
| Subject group type               | Reporting group                            | Reporting group         |  |  |
| Number of subjects analysed      | 189  | 64                      |  |  |
| Units: Months                    |  |                         |  |  |
| median (confidence interval 95%) | 15.18 (13.90 to 18.43)                     | 12.78 (9.86 to 15.38)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Objective Response Rate (ORR)

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) <sup>[3]</sup> |
|-----------------|--|

**End point description:**

The intent-to-treat (ITT) population included all Category 1 randomized participants, whether or not the assigned study treatment was received. Endpoints for Category 2 were exploratory and were not included in this analysis.

NA: Participants had no lesions to report at baseline

NE: Post-baseline assessments reported not evaluable for any reason or if SD assessment was within 6 weeks of baseline

Missing: No post-baseline assessments available

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

**End point timeframe:**

Two consecutive occurrences of complete or partial response  $\geq 4$  weeks apart

**Notes:**

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

Justification: Endpoints for Category 2 were exploratory and were not included in this analysis.

| <b>End point values</b>           | Molecularly-Guided Therapy MGT) Category 1 | Chemotherapy Category 1 |  |  |
|-----------------------------------|--|-------------------------|--|--|
| Subject group type                | Reporting group                            | Reporting group         |  |  |
| Number of subjects analysed       | 326  | 110                     |  |  |
| Units: Percentage of participants |  |                         |  |  |
| number (confidence interval 95%)  |  |                         |  |  |
| Complete response (CR)            | 4.9 (2.83 to 7.85)                         | 3.6 (1.00 to 9.05)      |  |  |
| Partial response (PR)             | 12.9 (9.45 to 17.01)                       | 4.5 (1.49 to 10.29)     |  |  |
| Stable disease (SD)               | 44.5 (39.00 to 50.06)                      | 49.1 (39.43 to 58.80)   |  |  |
| Non-CR/Non-PD                     | 7.1 (4.52 to 10.40)                        | 6.4 (2.60 to 12.67)     |  |  |
| NA                                | 2.5 (1.07 to 4.78)                         | 2.7 (0.57 to 7.76)      |  |  |
| Progressive disease (PD)          | 17.8 (13.80 to 22.38)                      | 21.8 (14.51 to 30.70)   |  |  |
| Not evaluable                     | 0.6 (0.07 to 2.20)                         | 0 (0.00 to 3.30)        |  |  |
| Missing                           | 9.8 (6.81 to 13.57)                        | 11.8 (6.45 to 19.36)    |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Duration of Response (DOR)**

|                 |   |
|-----------------|---|
| End point title | Duration of Response (DOR) <sup>[4]</sup> |
|-----------------|---|

**End point description:**

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

**End point timeframe:**

From the first documentation of a complete response (CR) or partial response (PR) to disease progression or death from any cause, whichever occurs first (up to approximately 70 months)



Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Endpoints for Category 2 were exploratory and were not included in this analysis.

| End point values                 | Molecularly-Guided Therapy MGT) Category 1 | Chemotherapy Category 1 |  |  |
|----------------------------------|--|-------------------------|--|--|
| Subject group type               | Reporting group                            | Reporting group         |  |  |
| Number of subjects analysed      | 58 <sup>[5]</sup>                          | 9 <sup>[6]</sup>        |  |  |
| Units: Months                    |  |                         |  |  |
| median (confidence interval 95%) | 16.39 (8.08 to 9999)                       | 9999 (4.14 to 9999)     |  |  |

Notes:

[5] - 9999 = Value is NA due to insufficient no. of participants with the event.

[6] - 9999 = Value is NA due to insufficient no. of participants with the event.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control Rate (DCR1)

|                 |  |
|-----------------|--|
| End point title | Disease Control Rate (DCR1) <sup>[7]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

From randomization to death from any cause, through the end of study (approximately 70 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Endpoints for Category 2 were exploratory and were not included in this analysis.

| End point values                 | Molecularly-Guided Therapy MGT) Category 1 | Chemotherapy Category 1 |  |  |
|----------------------------------|--|-------------------------|--|--|
| Subject group type               | Reporting group                            | Reporting group         |  |  |
| Number of subjects analysed      | 326  | 110                     |  |  |
| Units: Percentage of responders  |  |                         |  |  |
| number (confidence interval 95%) | 64.7 (59.27 to 69.91)                      | 60.0 (50.22 to 69.22)   |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Approximately 4.5 years

Adverse event reporting additional description:

All-cause mortality includes all participants.

The safety evaluable (SE) population (used to report serious and other AE) included all participants who received at least one dose of any component of study drug.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 27.1 |
|--------------------|------|

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Molecularly-Guided Therapy |
|-----------------------|----------------------------|

Reporting group description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study). MGT was chosen based on each participant's comprehensive genomic profile and administered until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Category 1 included participants with cancer of unknown primary site (CUP) with a complete response (CR), partial response (PR), or stable disease (SD) after 3 cycles of platinum induction chemotherapy (provided at the beginning of the study).

Participants in this arm continued to receive the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

|                       |            |
|-----------------------|------------|
| Reporting group title | Category 2 |
|-----------------------|------------|

Reporting group description:

Category 2 included participants with progressive disease (PD) after 3 cycles of platinum induction chemotherapy. Participants in this arm received either MGT based on their comprehensive genomic profile until loss of clinical benefit, unacceptable toxicity, participant or investigator decision to discontinue, or death, whichever occurred first, or the same chemotherapy regimen used during induction for a minimum of 3 additional cycles.

| Serious adverse events  | Molecularly-Guided Therapy | Chemotherapy      | Category 2       |
|---|----------------------------|-------------------|------------------|
| Total subjects affected by serious adverse events                   |                            |                   |                  |
| subjects affected / exposed   | 119 / 312 (38.14%)         | 15 / 102 (14.71%) | 39 / 93 (41.94%) |
| number of deaths (all causes)                                       | 227                        | 79                | 84               |
| number of deaths resulting from adverse events                      | 15                         | 0                 | 12               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                            |                   |                  |
| Cholangiocarcinoma  |                            |                   |                  |
| subjects affected / exposed   | 1 / 312 (0.32%)            | 0 / 102 (0.00%)   | 0 / 93 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1                      | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0                      | 0 / 0             | 0 / 0            |

|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| Prostatic adenoma                                    |                 |                 |                |
| subjects affected / exposed                          | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Tumour associated fever                              |                 |                 |                |
| subjects affected / exposed                          | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Vascular disorders                                   |                 |                 |                |
| Vena cava thrombosis                                 |                 |                 |                |
| subjects affected / exposed                          | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Shock haemorrhagic                                   |                 |                 |                |
| subjects affected / exposed                          | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypotension  |                 |                 |                |
| subjects affected / exposed                          | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Circulatory collapse                                 |                 |                 |                |
| subjects affected / exposed                          | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Thrombosis   |                 |                 |                |
| subjects affected / exposed                          | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                 |                 |                |
| Death  |                 |                 |                |
| subjects affected / exposed                          | 3 / 312 (0.96%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 3           | 0 / 0           | 0 / 1          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| General physical health deterioration           |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 1 / 102 (0.98%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pain  |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pyrexia   |                 |                 |                |
| subjects affected / exposed                     | 7 / 312 (2.24%) | 0 / 102 (0.00%) | 2 / 93 (2.15%) |
| occurrences causally related to treatment / all | 1 / 8           | 0 / 0           | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Oedema peripheral                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Fatigue   |                 |                 |                |
| subjects affected / exposed                     | 3 / 312 (0.96%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Immune system disorders                         |                 |                 |                |
| Drug hypersensitivity                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypersensitivity                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                |
| Dyspnoea  |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 2 / 93 (2.15%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 4          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Pneumonitis                                     |                 |                 |                |
| subjects affected / exposed                     | 4 / 312 (1.28%) | 2 / 102 (1.96%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4           | 2 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Interstitial lung disease                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Chronic obstructive pulmonary disease           |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary oedema                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory failure                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemoptysis                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pleural effusion                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 2 / 93 (2.15%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Psychiatric disorders                           |                 |                 |                |
| Suicide attempt                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| Psychiatric decompensation<br>subjects affected / exposed  | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0          |
| Anxiety<br>subjects affected / exposed   | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0          |
| Delirium<br>subjects affected / exposed  | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0          |
| Investigations<br>Neutrophil count decreased<br>subjects affected / exposed                      | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to<br>treatment / all   | 2 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0          |
| Liver function test abnormal<br>subjects affected / exposed                                      | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to<br>treatment / all   | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0          |
| Hepatic enzyme increased<br>subjects affected / exposed  | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to<br>treatment / all   | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0          |
| Electrocardiogram QT prolonged<br>subjects affected / exposed                                    | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to<br>treatment / all   | 3 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0          |
| Injury, poisoning and procedural<br>complications<br>Hip fracture<br>subjects affected / exposed | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Fall  |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Femoral neck fracture                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lumbar vertebral fracture                       |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Spinal compression fracture                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Stoma site haemorrhage                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Subdural haematoma                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Wrist fracture                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ankle fracture                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Procedural pain                                 |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac disorders                               |                 |                 |                |
| Myocardial infarction                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac failure                                 |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Endocarditis noninfective                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Acute myocardial infarction                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Cardiac arrest                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrial fibrillation                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 3 / 93 (3.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac failure chronic                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardio-respiratory arrest                       |                 |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Heart valve incompetence                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nervous system disorders                        |                 |                 |                |
| Cerebral haemorrhage                            |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Cerebral ischaemia                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Dysarthria                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peripheral sensory neuropathy                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Myasthenic syndrome                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0          |
| Mononeuritis                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Immune-mediated encephalitis                    |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hydrocephalus                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemorrhage intracranial                        |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Vestibular migraine                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Transient ischaemic attack                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Subarachnoid haemorrhage                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Seizure   |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ischaemic stroke                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 2 / 93 (2.15%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Syncope   |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |                |
| <b>Anaemia</b>                                  |                 |                 |                |
| subjects affected / exposed                     | 4 / 312 (1.28%) | 0 / 102 (0.00%) | 5 / 93 (5.38%) |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 0           | 5 / 5          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Febrile neutropenia</b>                      |                 |                 |                |
| subjects affected / exposed                     | 3 / 312 (0.96%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Neutropenia</b>                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Autoimmune haemolytic anaemia</b>            |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Bone marrow failure</b>                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0          |
| <b>Agranulocytosis</b>                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Pancytopenia</b>                             |                 |                 |                |
| subjects affected / exposed                     | 4 / 312 (1.28%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Thrombocytopenia</b>                         |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Thrombotic microangiopathy                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Eye disorders                                   |                 |                 |                |
| Periorbital oedema                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal disorders                      |                 |                 |                |
| Abdominal pain upper                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal incarcerated hernia                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal pain                                  |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Anal fistula                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Colitis   |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Constipation                                    |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 312 (0.32%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastric ulcer haemorrhage                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer perforation                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenitis                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diarrhoea                                       |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Intestinal obstruction                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nausea  |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Neutropenic colitis                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Small intestinal obstruction                    |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumatosis intestinalis                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Small intestinal haemorrhage                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Oesophageal varices haemorrhage                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Vomiting  |                 |                 |                |
| subjects affected / exposed                     | 6 / 312 (1.92%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 5 / 8           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ascites   |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemorrhoidal haemorrhage                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal pain lower                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ileus   |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Large intestinal haemorrhage                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hepatobiliary disorders                         |                 |                 |                |
| Cholecystitis                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gallbladder rupture                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Jaundice cholestatic                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cholestasis                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Acute cholecystitis necrotic                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                 |                 |                |
| Pruritus  |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rash maculo-papular                             |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal and urinary disorders                     |                 |                 |                |
| Acute kidney injury                             |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 2 / 102 (1.96%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Tubulointerstitial nephritis                    |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hydronephrosis                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal failure                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 2 / 93 (2.15%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Endocrine disorders                             |                 |                 |                |
| Hyperthyroidism                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Inappropriate antidiuretic hormone secretion    |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Secondary adrenocortical insufficiency          |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Musculoskeletal and connective tissue disorders |                 |                 |                |
| Arthritis                                       |                 |                 |                |
| subjects affected / exposed                     | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Spinal pain                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Myalgia   |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Back pain                                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Infections and infestations                     |                 |                 |                |
| Anal abscess                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| COVID-19  |                 |                 |                |
| subjects affected / exposed                     | 7 / 312 (2.24%) | 1 / 102 (0.98%) | 2 / 93 (2.15%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 1           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 2          |
| Peritonitis                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumonia                                       |                 |                 |                |
| subjects affected / exposed                     | 6 / 312 (1.92%) | 1 / 102 (0.98%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 2 / 6           | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Urinary tract infection                         |                 |                 |                |
| subjects affected / exposed                     | 6 / 312 (1.92%) | 0 / 102 (0.00%) | 2 / 93 (2.15%) |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Urosepsis                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 2 / 93 (2.15%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Sepsis  |                 |                 |                |
| subjects affected / exposed                     | 3 / 312 (0.96%) | 0 / 102 (0.00%) | 4 / 93 (4.30%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           | 1 / 4          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 3          |
| Abdominal abscess                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal infection                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abscess jaw                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Device related infection                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Clostridium difficile colitis                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cystitis  |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                                   | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Campylobacter gastroenteritis                                 |                 |                 |                |
| subjects affected / exposed                                   | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Encephalitis  |                 |                 |                |
| subjects affected / exposed                                   | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Escherichia sepsis  |                 |                 |                |
| subjects affected / exposed                                   | 0 / 312 (0.00%) | 1 / 102 (0.98%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |                |
| subjects affected / exposed                                   | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastroenteritis salmonella                                    |                 |                 |                |
| subjects affected / exposed                                   | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Infection   |                 |                 |                |
| subjects affected / exposed                                   | 3 / 312 (0.96%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all               | 1 / 3           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastroenteritis   |                 |                 |                |
| subjects affected / exposed                                   | 2 / 312 (0.64%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all               | 1 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0          |
| Lower respiratory tract infection                             |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peritonitis bacterial                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumonia bacterial                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Staphylococcal abscess                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pyonephrosis                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory tract infection viral               |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Post procedural infection                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Upper respiratory tract infection               |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory tract infection                     |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastroenteritis viral                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal sepsis                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Respiratory tract infection fungal              |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Wound infection                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Enterococcal infection                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ophthalmic herpes zoster                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Vascular device infection                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 312 (0.00%) | 0 / 102 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Metabolism and nutrition disorders              |                 |                 |                |
| Dehydration                                     |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diabetes mellitus                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hyponatraemia                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Type 1 diabetes mellitus                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 312 (0.32%) | 0 / 102 (0.00%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

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

| Non-serious adverse events                            | Molecularly-Guided Therapy | Chemotherapy      | Category 2       |
|---|----------------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events |                            |                   |                  |
| subjects affected / exposed                           | 279 / 312 (89.42%)         | 81 / 102 (79.41%) | 73 / 93 (78.49%) |
| Vascular disorders                                    |                            |                   |                  |
| Hypertension  |                            |                   |                  |
| subjects affected / exposed                           | 22 / 312 (7.05%)           | 3 / 102 (2.94%)   | 0 / 93 (0.00%)   |
| occurrences (all)                                     | 28                         | 3                 | 0                |
| General disorders and administration site conditions  |                            |                   |                  |
| Fatigue   |                            |                   |                  |
| subjects affected / exposed                           | 69 / 312 (22.12%)          | 14 / 102 (13.73%) | 22 / 93 (23.66%) |
| occurrences (all)                                     | 106                        | 19                | 28               |
| Oedema peripheral                                     |                            |                   |                  |
| subjects affected / exposed                           | 26 / 312 (8.33%)           | 3 / 102 (2.94%)   | 8 / 93 (8.60%)   |
| occurrences (all)                                     | 31                         | 6                 | 8                |
| Pyrexia   |                            |                   |                  |

|  |                         |                         |                        |
|--|-------------------------|-------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)   | 29 / 312 (9.29%)<br>46  | 4 / 102 (3.92%)<br>5    | 10 / 93 (10.75%)<br>10 |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                             | 60 / 312 (19.23%)<br>86 | 15 / 102 (14.71%)<br>19 | 15 / 93 (16.13%)<br>17 |
| Respiratory, thoracic and mediastinal disorders  |                         |                         |                        |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                             | 23 / 312 (7.37%)<br>33  | 4 / 102 (3.92%)<br>4    | 5 / 93 (5.38%)<br>6    |
| Cough<br>subjects affected / exposed<br>occurrences (all)                                | 23 / 312 (7.37%)<br>42  | 3 / 102 (2.94%)<br>3    | 0 / 93 (0.00%)<br>0    |
| Psychiatric disorders  |                         |                         |                        |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 17 / 312 (5.45%)<br>21  | 1 / 102 (0.98%)<br>1    | 5 / 93 (5.38%)<br>5    |
| Investigations   |                         |                         |                        |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)           | 33 / 312 (10.58%)<br>59 | 9 / 102 (8.82%)<br>13   | 9 / 93 (9.68%)<br>22   |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)             | 38 / 312 (12.18%)<br>78 | 9 / 102 (8.82%)<br>18   | 11 / 93 (11.83%)<br>15 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 20 / 312 (6.41%)<br>20  | 3 / 102 (2.94%)<br>3    | 6 / 93 (6.45%)<br>7    |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 17 / 312 (5.45%)<br>26  | 7 / 102 (6.86%)<br>7    | 0 / 93 (0.00%)<br>0    |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 19 / 312 (6.09%)<br>23  | 6 / 102 (5.88%)<br>6    | 0 / 93 (0.00%)<br>0    |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)           | 16 / 312 (5.13%)<br>18  | 1 / 102 (0.98%)<br>1    | 0 / 93 (0.00%)<br>0    |
| White blood cell count decreased   |                         |                         |                        |

|  |                           |                         |                        |
|--|---------------------------|-------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 312 (0.00%)<br>0      | 0 / 102 (0.00%)<br>0    | 6 / 93 (6.45%)<br>7    |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 17 / 312 (5.45%)<br>20    | 1 / 102 (0.98%)<br>1    | 0 / 93 (0.00%)<br>0    |
| Nervous system disorders   |                           |                         |                        |
| Headache<br>subjects affected / exposed<br>occurrences (all)                             | 19 / 312 (6.09%)<br>21    | 3 / 102 (2.94%)<br>5    | 0 / 93 (0.00%)<br>0    |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)        | 21 / 312 (6.73%)<br>25    | 7 / 102 (6.86%)<br>8    | 0 / 93 (0.00%)<br>0    |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                | 39 / 312 (12.50%)<br>46   | 15 / 102 (14.71%)<br>18 | 0 / 93 (0.00%)<br>0    |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                            | 17 / 312 (5.45%)<br>21    | 3 / 102 (2.94%)<br>3    | 0 / 93 (0.00%)<br>0    |
| Blood and lymphatic system disorders   |                           |                         |                        |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                           | 16 / 312 (5.13%)<br>26    | 9 / 102 (8.82%)<br>15   | 5 / 93 (5.38%)<br>5    |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                          | 62 / 312 (19.87%)<br>100  | 24 / 102 (23.53%)<br>41 | 11 / 93 (11.83%)<br>13 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                     | 49 / 312 (15.71%)<br>80   | 14 / 102 (13.73%)<br>25 | 13 / 93 (13.98%)<br>20 |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                              | 111 / 312 (35.58%)<br>180 | 30 / 102 (29.41%)<br>37 | 37 / 93 (39.78%)<br>55 |
| Gastrointestinal disorders   |                           |                         |                        |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                       | 35 / 312 (11.22%)<br>40   | 3 / 102 (2.94%)<br>3    | 10 / 93 (10.75%)<br>11 |
| Vomiting   |                           |                         |                        |



|   |                   |                   |                  |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed                     | 41 / 312 (13.14%) | 13 / 102 (12.75%) | 10 / 93 (10.75%) |
| occurrences (all)                               | 58                | 17                | 12               |
| Diarrhoea                                       |                   |                   |                  |
| subjects affected / exposed                     | 76 / 312 (24.36%) | 6 / 102 (5.88%)   | 9 / 93 (9.68%)   |
| occurrences (all)                               | 118               | 8                 | 11               |
| Constipation                                    |                   |                   |                  |
| subjects affected / exposed                     | 43 / 312 (13.78%) | 12 / 102 (11.76%) | 14 / 93 (15.05%) |
| occurrences (all)                               | 55                | 13                | 15               |
| Nausea  |                   |                   |                  |
| subjects affected / exposed                     | 88 / 312 (28.21%) | 20 / 102 (19.61%) | 23 / 93 (24.73%) |
| occurrences (all)                               | 127               | 34                | 36               |
| Abdominal pain upper                            |                   |                   |                  |
| subjects affected / exposed                     | 19 / 312 (6.09%)  | 5 / 102 (4.90%)   | 0 / 93 (0.00%)   |
| occurrences (all)                               | 21                | 5                 | 0                |
| Skin and subcutaneous tissue disorders          |                   |                   |                  |
| Rash  |                   |                   |                  |
| subjects affected / exposed                     | 35 / 312 (11.22%) | 2 / 102 (1.96%)   | 0 / 93 (0.00%)   |
| occurrences (all)                               | 48                | 5                 | 0                |
| Pruritus  |                   |                   |                  |
| subjects affected / exposed                     | 28 / 312 (8.97%)  | 1 / 102 (0.98%)   | 0 / 93 (0.00%)   |
| occurrences (all)                               | 43                | 1                 | 0                |
| Alopecia  |                   |                   |                  |
| subjects affected / exposed                     | 24 / 312 (7.69%)  | 1 / 102 (0.98%)   | 0 / 93 (0.00%)   |
| occurrences (all)                               | 24                | 1                 | 0                |
| Endocrine disorders                             |                   |                   |                  |
| Hypothyroidism                                  |                   |                   |                  |
| subjects affected / exposed                     | 20 / 312 (6.41%)  | 0 / 102 (0.00%)   | 5 / 93 (5.38%)   |
| occurrences (all)                               | 20                | 0                 | 5                |
| Musculoskeletal and connective tissue disorders |                   |                   |                  |
| Back pain                                       |                   |                   |                  |
| subjects affected / exposed                     | 26 / 312 (8.33%)  | 2 / 102 (1.96%)   | 8 / 93 (8.60%)   |
| occurrences (all)                               | 34                | 3                 | 9                |
| Myalgia   |                   |                   |                  |
| subjects affected / exposed                     | 21 / 312 (6.73%)  | 7 / 102 (6.86%)   | 0 / 93 (0.00%)   |
| occurrences (all)                               | 29                | 7                 | 0                |
| Arthralgia                                      |                   |                   |                  |

|   |                         |                        |                        |
|---|-------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 52 / 312 (16.67%)<br>67 | 6 / 102 (5.88%)<br>6   | 6 / 93 (6.45%)<br>9    |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                     | 21 / 312 (6.73%)<br>35  | 3 / 102 (2.94%)<br>3   | 0 / 93 (0.00%)<br>0    |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 312 (0.00%)<br>0    | 0 / 102 (0.00%)<br>0   | 6 / 93 (6.45%)<br>6    |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all)               | 27 / 312 (8.65%)<br>28  | 2 / 102 (1.96%)<br>2   | 5 / 93 (5.38%)<br>5    |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                               | 29 / 312 (9.29%)<br>36  | 5 / 102 (4.90%)<br>6   | 0 / 93 (0.00%)<br>0    |
| Metabolism and nutrition disorders<br>Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all) | 22 / 312 (7.05%)<br>37  | 5 / 102 (4.90%)<br>7   | 6 / 93 (6.45%)<br>7    |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                                    | 60 / 312 (19.23%)<br>74 | 10 / 102 (9.80%)<br>12 | 14 / 93 (15.05%)<br>17 |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 312 (0.00%)<br>0    | 0 / 102 (0.00%)<br>0   | 5 / 93 (5.38%)<br>5    |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 312 (0.00%)<br>0    | 0 / 102 (0.00%)<br>0   | 5 / 93 (5.38%)<br>5    |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 312 (0.00%)<br>0    | 0 / 102 (0.00%)<br>0   | 7 / 93 (7.53%)<br>7    |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 06 May 2018      | Amended eligibility criteria.   |
| 13 July 2018     | Updated eligibility criteria.   |
| 05 November 2018 | Amended eligibility criteria.   |
| 29 July 2019     | Added a new treatment (entrectinib). Replaced ipatasertib monotherapy with ipatasertib + paclitaxel combination therapy. Amended eligibility criteria.  |
| 11 February 2020 | Amended eligibility criteria. Added the option for additional chemotherapy for eligible participants. Re-added ipatasertib monotherapy for participants that had started ipatasertib monotherapy under previous protocol versions.  |
| 19 February 2021 | Added pemigatinib and ivosidenib as treatments. Replaced duration of clinical benefit endpoint with duration of response (DOR) and disease control rate (DCR). Category 1 participants deemed ineligible for MGT were allowed to continue with platinum-based chemotherapy. Amended eligibility criteria. |
| 16 August 2021   | Change to olaparib dose and formulation. Amended eligibility criteria.  |
| 24 January 2022  | Addition of efficacy analysis population for Category 2 participants.   |
| 15 February 2023 | Removed patient reported outcomes for participants continuing treatment beyond disease progression. Updated study duration. Replaced "Wegener granulomatosis" with "granulomatosis with polyangiitis" to align with updates to MedDRA.  |
| 09 March 2024    | Added a section for an extension part of the study for patients with no post-trial access to the investigational medicinal products (IMPs), and to provide continued access to patients until disease progression or loss of clinical benefit.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported