



## Clinical trial results:

**A randomized Phase III, double-blind, placebo-controlled multicenter trial of daily everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer**

### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2008-008697-31                |
| Trial protocol           | DE GR BE IT ES FR CZ GB HU SK |
| Global end of trial date | 11 June 2015                  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 27 June 2016 |
| First version publication date | 27 June 2016 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRAD001W2301 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01007942 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 11 June 2015 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 11 June 2015 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the combination of everolimus, vinorelbine and trastuzumab to the combination of vinorelbine and trastuzumab with respect to progression-free survival, based on local radiological review, in women with HER2/neu overexpressing advanced or metastatic breast cancer who are resistant to trastuzumab and have been pre-treated with a taxane.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 20 October 2009 |
| 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 | Argentina: 32      |
| Country: Number of subjects enrolled | Australia: 21      |
| Country: Number of subjects enrolled | Belgium: 18        |
| Country: Number of subjects enrolled | China: 49          |
| Country: Number of subjects enrolled | Czech Republic: 10 |
| Country: Number of subjects enrolled | France: 29         |
| Country: Number of subjects enrolled | Germany: 37        |
| Country: Number of subjects enrolled | United Kingdom: 29 |
| Country: Number of subjects enrolled | Greece: 16         |
| Country: Number of subjects enrolled | Hungary: 30        |
| Country: Number of subjects enrolled | Israel: 17         |
| Country: Number of subjects enrolled | Italy: 19          |
| Country: Number of subjects enrolled | Japan: 57          |
| Country: Number of subjects enrolled | Mexico: 4          |
| Country: Number of subjects enrolled | Poland: 1          |
| Country: Number of subjects enrolled | Singapore: 12      |
| Country: Number of subjects enrolled | Slovakia: 2        |
| Country: Number of subjects enrolled | Spain: 32          |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Thailand: 7        |
| Country: Number of subjects enrolled | Turkey: 24         |
| Country: Number of subjects enrolled | United States: 123 |
| Worldwide total number of subjects   | 569                |
| EEA total number of subjects         | 223                |

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)                      | 472 |
| From 65 to 84 years                       | 97  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

DCO ( Data cut-off) for patient disposition is 1-Apr-2015. Each Cycle = 21 days.

Patients completed = on treatment at time of DCO. Not Completed = ended treatment as per protocol.

### Pre-assignment

Screening details:

284 patients were randomized to the Everolimus + trastuzumab +vinorelbine arm but only 280 took drug. 285 were randomized to the placebo + trastuzumab + vinorelbine arm but only 282 took drug.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes                                    |
| <b>Arm title</b>             | Everolimus + vinorelbine + trastuzumab |

Arm description:

Oral everolimus (5 mg/day) + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | everolimus   |
| Investigational medicinal product code | RAD001       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Oral everolimus (5 mg/day) packaged in blister packs.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | trastuzumab     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

Dosage and administration details:

intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)

|  |                 |
|--|-----------------|
| Investigational medicinal product name | vinorelbine     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

Dosage and administration details:

intravenous vinorelbine (25 mg/m2 weekly)

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | placebo + vinorelbine + trastuzumab |
|------------------|-------------------------------------|

Arm description:

Oral daily matching placebo + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |                    |
|--|--------------------|
| Investigational medicinal product name | everolimus placebo |
| Investigational medicinal product code | RAD001             |
| Other name                             |                    |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

Oral everolimus placebo (5 mg/day) packaged in blister packs.

| <b>Number of subjects in period 1</b> | Everolimus +<br>vinorelbine +<br>trastuzumab | placebo +<br>vinorelbine +<br>trastuzumab |
|---------------------------------------|--|---|
| Started                               | 284  | 285                                       |
| Completed                             | 3  | 7   |
| Not completed                         | 281  | 278                                       |
| Adverse event, serious fatal          | 3  | 2   |
| Consent withdrawn by subject          | 19   | 14  |
| Disease progression                   | 217  | 242                                       |
| Abnormal test procedure               | -  | 1   |
| Adverse event, non-fatal              | 29   | 14  |
| New cancer therapy                    | 5  | 1   |
| Administrative problems               | 2  | -   |
| Patients Untreated                    | 4  | 3   |
| Lost to follow-up                     | 1  | -   |
| Protocol deviation                    | 1  | 1   |

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | Everolimus + vinorelbine + trastuzumab |
| Reporting group description:   |  |
| Oral everolimus (5 mg/day) + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)  |  |
| Reporting group title  | placebo + vinorelbine + trastuzumab    |
| Reporting group description:   |  |
| Oral daily matching placebo + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only) |  |

| Reporting group values                                | Everolimus +<br>vinorelbine +<br>trastuzumab | placebo +<br>vinorelbine +<br>trastuzumab | Total |
|---|--|---|-------|
| Number of subjects                                    | 284  | 285                                       | 569   |
| Age categorical<br>Units: Subjects                    |  |   |       |
| In utero  | 0  | 0   | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0  | 0   | 0     |
| Newborns (0-27 days)                                  | 0  | 0   | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0  | 0   | 0     |
| Children (2-11 years)                                 | 0  | 0   | 0     |
| Adolescents (12-17 years)                             | 0  | 0   | 0     |
| Adults (18-64 years)                                  | 230  | 242                                       | 472   |
| From 65-84 years                                      | 54   | 43  | 97    |
| 85 years and over                                     | 0  | 0   | 0     |
| Age Continuous<br>Units: years                        |  |   |       |
| arithmetic mean                                       | 54.3   | 53.4                                      |       |
| standard deviation                                    | ± 10.98                                      | ± 11                                      | -     |
| Gender, Male/Female<br>Units: Participants            |  |   |       |
| Female  | 284  | 285                                       | 569   |
| Male  | 0  | 0   | 0     |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Everolimus + vinorelbine + trastuzumab               |
| Reporting group description:<br>Oral everolimus (5 mg/day) + intravenous vinorelbine (25 mg/m <sup>2</sup> weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)  |  |
| Reporting group title  | placebo + vinorelbine + trastuzumab                  |
| Reporting group description:<br>Oral daily matching placebo + intravenous vinorelbine (25 mg/m <sup>2</sup> weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only) |  |
| Subject analysis set title   | Everolimus 2.5 mg                                    |
| Subject analysis set type  | Sub-group analysis                                   |
| Subject analysis set description:<br>Oral everolimus of 2.5 mg/day   |  |
| Subject analysis set title   | Everolimus 5mg/day                                   |
| Subject analysis set type  | Sub-group analysis                                   |
| Subject analysis set description:<br>Oral everolimus of 5 mg/day   |  |
| Subject analysis set title   | Everolimus (Vinorelbine blood concentration)         |
| Subject analysis set type  | Sub-group analysis                                   |
| Subject analysis set description:<br>Oral everolimus of 5 mg/day   |  |
| Subject analysis set title   | Everolimus Placebo (Vinorelbine blood concentration) |
| Subject analysis set type  | Sub-group analysis                                   |
| Subject analysis set description:<br>Oral placebo everolimus of 5 mg/day   |  |
| Subject analysis set title   | Everolimus (trastuzumab serum concentration)         |
| Subject analysis set type  | Sub-group analysis                                   |
| Subject analysis set description:<br>Oral everolimus of 5 mg/day   |  |
| Subject analysis set title   | Everolimus Placebo (trastuzumab serum concentration) |
| Subject analysis set type  | Sub-group analysis                                   |
| Subject analysis set description:<br>Oral placebo everolimus of 5 mg/day   |  |

### Primary: Progressive-free survival (PFS) per Investigator assessment

|  |   |
|--|---|
| End point title  | Progressive-free survival (PFS) per Investigator assessment |
| End point description:<br>PFS was defined as the time from the date of randomization to the date of first radiologically documented tumor progression or death from any cause, whichever occurs first. PFS primary analysis performed when 415 events were reached |   |
| End point type   | Primary   |
| End point timeframe:<br>Every 6 weeks until disease progression or death which ever occurred first up to 15-Mar-2013   |   |

| End point values                 | Everolimus +<br>vinorelbine +<br>trastuzumab | placebo +<br>vinorelbine +<br>trastuzumab |  |  |
|----------------------------------|--|---|--|--|
| Subject group type               | Reporting group                              | Reporting group                           |  |  |
| Number of subjects analysed      | 284  | 285                                       |  |  |
| Units: months                    |  |   |  |  |
| median (confidence interval 95%) | 7 (6.74 to<br>8.18)                          | 5.78 (5.49 to<br>6.9)                     |  |  |

## Statistical analyses

| Statistical analysis title              | Comparison of the distribution of PFS   |
|---|---|
| Comparison groups                       | Everolimus + vinorelbine + trastuzumab v placebo +<br>vinorelbine + trastuzumab |
| Number of subjects included in analysis | 569   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0067  |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.78  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.65  |
| upper limit                             | 0.95  |

## Secondary: Overall survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall survival (OS) |
| End point description:  |                       |
| OS was defined as the time from date of randomization to the date of death from any cause. Final OS was conducted when 388 deaths occurred. |                       |
| End point type  | Secondary             |
| End point timeframe:  |                       |
| Every 3 months until death up to 1-Apr-2015   |                       |

| End point values                 | Everolimus +<br>vinorelbine +<br>trastuzumab | placebo +<br>vinorelbine +<br>trastuzumab |  |  |
|----------------------------------|--|---|--|--|
| Subject group type               | Reporting group                              | Reporting group                           |  |  |
| Number of subjects analysed      | 284  | 285                                       |  |  |
| Units: months                    |  |   |  |  |
| median (confidence interval 95%) | 23.46 (20.01<br>to 28.81)                    | 24.08 (21.49<br>to 27.63)                 |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall response rate (ORR)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Overall response rate (ORR) |
|-----------------|-----------------------------|

End point description:

ORR was defined as the percentage of participants whose best overall response was either complete response (CR) or partial response (PR) according to RECIST version 1.0

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

End point timeframe:

Every 6 weeks until disease progression or death which ever occurred first up to 15-Mar-2013

| End point values                  | Everolimus +<br>vinorelbine +<br>trastuzumab | placebo +<br>vinorelbine +<br>trastuzumab |  |  |
|-----------------------------------|--|---|--|--|
| Subject group type                | Reporting group                              | Reporting group                           |  |  |
| Number of subjects analysed       | 284  | 285                                       |  |  |
| Units: Percentage of participants |  |   |  |  |
| number (confidence interval 95%)  | 40.8 (35.1 to<br>46.8)                       | 37.2 (31.6 to<br>43.1)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical benefit rate (CBR)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Clinical benefit rate (CBR) |
|-----------------|-----------------------------|

End point description:

CBR was defined as the percentage of participants whose best overall response, according to RECIST, was either complete response (CR), a partial response (PR) or stable disease (SD) lasting for at least 24 weeks.

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

End point timeframe:

Every 6 weeks until disease progression or death which ever occurred first up to 15-Mar-2013

| End point values                  | Everolimus +<br>vinorelbine +<br>trastuzumab | placebo +<br>vinorelbine +<br>trastuzumab |  |  |
|-----------------------------------|--|---|--|--|
| Subject group type                | Reporting group                              | Reporting group                           |  |  |
| Number of subjects analysed       | 284  | 285                                       |  |  |
| Units: Percentage of participants |  |   |  |  |
| number (confidence interval 95%)  | 59.2 (53.2 to<br>64.9)                       | 53.3 (47.4 to<br>59.2)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to deterioration of the ECOG performance status score

|   |  |
|---|--|
| End point title   | Time to deterioration of the ECOG performance status score |
| End point description:<br>The Time to deterioration of the ECOG performance status score was summarized at the time of each assessment. |  |
| End point type  | Secondary  |
| End point timeframe:<br>baseline, until disease progression or death up to 15-Mar-2013  |  |

| End point values            | Everolimus +<br>vinorelbine +<br>trastuzumab | placebo +<br>vinorelbine +<br>trastuzumab |  |  |
|-----------------------------|--|---|--|--|
| Subject group type          | Reporting group                              | Reporting group                           |  |  |
| Number of subjects analysed | 284  | 285                                       |  |  |
| Units: months               |  |   |  |  |
| number (not applicable)     | 32.66  | 21.55                                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: PRO: Time to deterioration in global health status/QoL domain score of the European Organization for the Research and Treatment of Cancer (EORTC)-Core Quality of Life Questionnaire (QLQ-C30) (by at least 10%)

|                 |  |
|-----------------|--|
| End point title | PRO: Time to deterioration in global health status/QoL domain score of the European Organization for the Research and Treatment of Cancer (EORTC)-Core Quality of Life Questionnaire (QLQ-C30) (by at least 10%) |
|-----------------|--|

End point description:

PRO = patient reported outcomes; Time to deterioration ( $\geq 10\%$  worsening from baseline), in the global health status of EORTC QLQ-C30 scale was done in the 3 functional scales (emotional, physical, & social functioning [EF, PF, & SF]). It contains 30 items & is composed of multi-item scales & single-item measures. These include 5 functional scales (physical, role, emotional, social & cognitive functioning), 3 symptom scales (fatigue, pain, nausea, & vomiting), a global health status/QoL scale, and 6 single items (dyspnea, diarrhea, constipation, anorexia, insomnia & financial impact). Each of the multi-item scale

includes a different set of items - no item occurs in more than 1 scale. Each item in the EORTC QLQ-C30 has 4 response categories (1=Not at all, 2= A little, 3= Quite a bit, 4= Very much) with the higher number representing a worse outcome. The global health domain score of the QLQ-C30 questionnaire was pre-specified as the primary QoL domain of interest & disclosed here.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline, until disease progression or death up to 15-Mar-2013 |           |

| End point values                                  | Everolimus + vinorelbine + trastuzumab | placebo + vinorelbine + trastuzumab |  |  |
|---|--|-------------------------------------|--|--|
| Subject group type                                | Reporting group                        | Reporting group                     |  |  |
| Number of subjects analysed                       | 284                                    | 285                                 |  |  |
| Units: months                                     |  |                                     |  |  |
| median (confidence interval 95%)                  |  |                                     |  |  |
| Deterioration - global QoL domain by at least 10% | 8.31 (6.93 to 11.53)                   | 7.29 (5.55 to 10.38)                |  |  |
| Deterioration in the PF domain by at least 10%    | 11.96 (8.31 to 14.09)                  | 12.48 (8.31 to 20.86)               |  |  |
| Deterioration in the EF domain by at least 10%    | 15.18 (9.2 to 17.28)                   | 12.45 (9.69 to 16.36)               |  |  |
| Deterioration in the SF domain by at least 10%    | 11.33 (8.18 to 14.52)                  | 13.11 (8.31 to 19.32)               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Everolimus blood concentrations by leading dose and time point

|  |  |
|--|--|
| End point title  | Everolimus blood concentrations by leading dose and time point |
| End point description:   |  |
| Pre-dose (Cmin) and 2 hours post-dose (C2h) everolimus PK blood samples were collected at Cycle 2 Day 1. Only valid everolimus PK blood samples collected at steady state were used in the analyses. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Cycle 2, Day 1   |  |

| End point values                             | Everolimus 2.5 mg    | Everolimus 5mg/day   |  |  |
|--|----------------------|----------------------|--|--|
| Subject group type                           | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                  | 10                   | 43                   |  |  |
| Units: ng/ml                                 |                      |                      |  |  |
| arithmetic mean (standard deviation)         |                      |                      |  |  |
| Pre-dose (Cmin) (n: 7, 32)                   | 2.928 (± 2.6197)     | 5.652 (± 4.1006)     |  |  |
| 2 hours post administration (C2h) (n:10, 43) | 13.035 (± 6.6842)    | 22.005 (± 13.38)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Vinorelbine blood concentrations by leading dose and time point

|                 |   |
|-----------------|---|
| End point title | Vinorelbine blood concentrations by leading dose and time point |
|-----------------|---|

End point description:

Pre-infusion (Cmin) and end of infusion (C2h) vinorelbine PK blood samples were collected at Cycle 2 Day 1. Only valid vinorelbine PK blood samples collected at steady state were used in the analyses.

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

End point timeframe:

Cycle 2, Day 1

| End point values                       | Everolimus<br>(Vinorelbine<br>blood<br>concentration) | Everolimus<br>Placebo<br>(Vinorelbine<br>blood<br>concentration) |  |  |
|--|---|--|--|--|
| Subject group type                     | Subject analysis set                                  | Subject analysis set   |  |  |
| Number of subjects analysed            | 76  | 64   |  |  |
| Units: ng/ml                           |   |  |  |  |
| arithmetic mean (standard deviation)   |   |  |  |  |
| Pre-infusion - dose (Cmin) (n: 76, 64) | 11.085 (±<br>66.8551)                                 | 0.061 (±<br>0.4888)  |  |  |
| End of infusion (Cmax) (n: 58, 49)     | 867.147 (±<br>971.3057)                               | 1068.51 (±<br>1145.86)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Trastuzumab blood concentrations by leading dose and time point

|                 |   |
|-----------------|---|
| End point title | Trastuzumab blood concentrations by leading dose and time point |
|-----------------|---|

End point description:

Pre-infusion (Cmin) and end of infusion (C2h) trastuzumab PK blood samples were collected at Cycle 3 Day 1. Only valid trastuzumab PK blood samples collected at steady state were used in the analyses.

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

End point timeframe:

Cycle 3, Day 1

| <b>End point values</b>                | Everolimus<br>(trastuzumab<br>serum<br>concentration) | Everolimus<br>Placebo<br>(trastuzumab<br>serum<br>concentration) |  |  |
|--|---|--|--|--|
| Subject group type                     | Subject analysis set                                  | Subject analysis set   |  |  |
| Number of subjects analysed            | 74  | 59   |  |  |
| Units: ng/ml                           |   |  |  |  |
| arithmetic mean (standard deviation)   |   |  |  |  |
| Pre-infusion - dose (Cmin) (n: 73, 57) | 23.351 (±<br>6.3344)                                  | 24.526 (±<br>7.996)  |  |  |
| End of infusion (Cmax) (n: 75, 59)     | 64.279 (±<br>27.8549)                                 | 60.576 (±<br>15.5198)  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Everolimus + trastuzumab + vinorelbine |
|-----------------------|--|

Reporting group description:

Everolimus + trastuzumab + vinorelbine

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Placebo + trastuzumab + vinorelbine |
|-----------------------|-------------------------------------|

Reporting group description:

Placebo + trastuzumab + vinorelbine

| Serious adverse events  | Everolimus +<br>trastuzumab +<br>vinorelbine | Placebo +<br>trastuzumab +<br>vinorelbine |  |
|---|--|---|--|
| Total subjects affected by serious adverse events                   |  |   |  |
| subjects affected / exposed   | 122 / 280 (43.57%)                           | 58 / 282 (20.57%)                         |  |
| number of deaths (all causes)                                       | 7  | 7   |  |
| number of deaths resulting from adverse events                      | 1  | 0   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |   |  |
| Metastases to central nervous system                                |  |   |  |
| subjects affected / exposed   | 1 / 280 (0.36%)                              | 1 / 282 (0.35%)                           |  |
| occurrences causally related to treatment / all                     | 0 / 1  | 0 / 1                                     |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                                     |  |
| Paraneoplastic syndrome   |  |   |  |
| subjects affected / exposed   | 1 / 280 (0.36%)                              | 0 / 282 (0.00%)                           |  |
| occurrences causally related to treatment / all                     | 0 / 1  | 0 / 0                                     |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                                     |  |
| Thyroid cancer  |  |   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| Deep vein thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Haematoma  |                 |                 |  |
| subjects affected / exposed                          | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Haemorrhage  |                 |                 |  |
| subjects affected / exposed                          | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypotension  |                 |                 |  |
| subjects affected / exposed                          | 1 / 280 (0.36%) | 2 / 282 (0.71%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Shock  |                 |                 |  |
| subjects affected / exposed                          | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Thrombosis   |                 |                 |  |
| subjects affected / exposed                          | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Chills  |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device dislocation                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Extravasation                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General physical health deterioration           |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 2 / 282 (0.71%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperpyrexia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperthermia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inflammation                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia   |                 |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 13 / 280 (4.64%) | 5 / 282 (1.77%) |  |
| occurrences causally related to treatment / all | 5 / 14           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Systemic inflammatory response syndrome         |                  |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%)  | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Reproductive system and breast disorders        |                  |                 |  |
| Breast pain                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%)  | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ovarian cyst                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%)  | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pelvic pain                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%)  | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Uterine haemorrhage                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%)  | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                  |                 |  |
| Acute respiratory distress syndrome             |                  |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%)  | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0           |  |
| Cough   |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%) | 2 / 282 (0.71%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 3 / 282 (1.06%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea exertional                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemothorax                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oropharyngeal pain                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%) | 5 / 282 (1.77%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 3 / 282 (1.06%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary arterial hypertension                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 5 / 282 (1.77%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 3 / 282 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachypnoea                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Suicide attempt                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Neutrophil count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fractured sacrum                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hand fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural pain                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound dehiscence                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Brain oedema                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disturbance in attention                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydrocephalus                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 3 / 282 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Migraine  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuralgia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neurological symptom                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathy peripheral                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |

|   |                   |                 |  |
|---|-------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%)   | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Somnolence                                      |                   |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%)   | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Blood and lymphatic system disorders            |                   |                 |  |
| Agranulocytosis                                 |                   |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%)   | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Anaemia   |                   |                 |  |
| subjects affected / exposed                     | 10 / 280 (3.57%)  | 2 / 282 (0.71%) |  |
| occurrences causally related to treatment / all | 22 / 22           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Febrile neutropenia                             |                   |                 |  |
| subjects affected / exposed                     | 30 / 280 (10.71%) | 4 / 282 (1.42%) |  |
| occurrences causally related to treatment / all | 28 / 31           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Immune thrombocytopenic purpura                 |                   |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%)   | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Leukopenia                                      |                   |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%)   | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Neutropenia                                     |                   |                 |  |
| subjects affected / exposed                     | 12 / 280 (4.29%)  | 3 / 282 (1.06%) |  |
| occurrences causally related to treatment / all | 13 / 14           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Thrombocytopenia                                |                   |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 280 (1.43%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Cataract  |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cataract subcapsular                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vision blurred                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 280 (1.79%) | 2 / 282 (0.71%) |  |
| occurrences causally related to treatment / all | 2 / 5           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphagia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric perforation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal inflammation                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic colitis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 9 / 280 (3.21%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 9 / 9           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 5 / 280 (1.79%) | 2 / 282 (0.71%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct obstruction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 2 / 282 (0.71%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic mass                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatocellular injury                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysuria   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flank pain                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neck pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abscess jaw                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspergillus infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchiolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 280 (1.43%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Conjunctivitis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 280 (1.07%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Furuncle  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis clostridial                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella bacteraemia                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lobar pneumonia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parainfluenzae virus infection                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonsillar abscess                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngitis                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumocystis jirovecii infection                |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 8 / 280 (2.86%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 3 / 8           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomonal sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 280 (1.07%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinusitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Soft tissue infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tuberculosis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 2 / 282 (0.71%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral upper respiratory tract infection         |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Cachexia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Decreased appetite                              |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypocalcaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 280 (0.00%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 280 (0.71%) | 1 / 282 (0.35%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Type 2 diabetes mellitus                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 280 (0.36%) | 0 / 282 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Everolimus +<br>trastuzumab +<br>vinorelbine | Placebo +<br>trastuzumab +<br>vinorelbine |  |
|---|--|---|--|
| Total subjects affected by non-serious adverse events |  |   |  |
| subjects affected / exposed                           | 280 / 280<br>(100.00%)                       | 280 / 282 (99.29%)                        |  |
| Investigations  |  |   |  |
| Alanine aminotransferase increased                    |  |   |  |
| subjects affected / exposed                           | 37 / 280 (13.21%)                            | 26 / 282 (9.22%)                          |  |
| occurrences (all)                                     | 49   | 46  |  |
| Aspartate aminotransferase increased                  |  |   |  |
| subjects affected / exposed                           | 33 / 280 (11.79%)                            | 22 / 282 (7.80%)                          |  |
| occurrences (all)                                     | 49   | 34  |  |
| Ejection fraction decreased                           |  |   |  |
| subjects affected / exposed                           | 17 / 280 (6.07%)                             | 5 / 282 (1.77%)                           |  |
| occurrences (all)                                     | 22   | 5   |  |
| Gamma-glutamyltransferase increased                   |  |   |  |
| subjects affected / exposed                           | 29 / 280 (10.36%)                            | 23 / 282 (8.16%)                          |  |
| occurrences (all)                                     | 34   | 31  |  |
| Haemoglobin decreased                                 |  |   |  |
| subjects affected / exposed                           | 22 / 280 (7.86%)                             | 18 / 282 (6.38%)                          |  |
| occurrences (all)                                     | 63   | 47  |  |
| Neutrophil count decreased                            |  |   |  |
| subjects affected / exposed                           | 14 / 280 (5.00%)                             | 8 / 282 (2.84%)                           |  |
| occurrences (all)                                     | 90   | 32  |  |
| Weight decreased                                      |  |   |  |
| subjects affected / exposed                           | 83 / 280 (29.64%)                            | 47 / 282 (16.67%)                         |  |
| occurrences (all)                                     | 99   | 62  |  |
| White blood cell count decreased                      |  |   |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 17 / 280 (6.07%)<br>104 | 23 / 282 (8.16%)<br>112 |  |
| Vascular disorders                               |                         |                         |  |
| Hot flush  |                         |                         |  |
| subjects affected / exposed                      | 4 / 280 (1.43%)         | 16 / 282 (5.67%)        |  |
| occurrences (all)                                | 4                       | 16                      |  |
| Hypertension                                     |                         |                         |  |
| subjects affected / exposed                      | 24 / 280 (8.57%)        | 10 / 282 (3.55%)        |  |
| occurrences (all)                                | 29                      | 12                      |  |
| Phlebitis  |                         |                         |  |
| subjects affected / exposed                      | 14 / 280 (5.00%)        | 18 / 282 (6.38%)        |  |
| occurrences (all)                                | 19                      | 23                      |  |
| Nervous system disorders                         |                         |                         |  |
| Dizziness  |                         |                         |  |
| subjects affected / exposed                      | 31 / 280 (11.07%)       | 24 / 282 (8.51%)        |  |
| occurrences (all)                                | 35                      | 30                      |  |
| Dysgeusia  |                         |                         |  |
| subjects affected / exposed                      | 32 / 280 (11.43%)       | 17 / 282 (6.03%)        |  |
| occurrences (all)                                | 37                      | 18                      |  |
| Headache   |                         |                         |  |
| subjects affected / exposed                      | 74 / 280 (26.43%)       | 62 / 282 (21.99%)       |  |
| occurrences (all)                                | 105                     | 98                      |  |
| Hypoaesthesia                                    |                         |                         |  |
| subjects affected / exposed                      | 15 / 280 (5.36%)        | 7 / 282 (2.48%)         |  |
| occurrences (all)                                | 17                      | 9                       |  |
| Neuropathy peripheral                            |                         |                         |  |
| subjects affected / exposed                      | 27 / 280 (9.64%)        | 41 / 282 (14.54%)       |  |
| occurrences (all)                                | 32                      | 47                      |  |
| Paraesthesia                                     |                         |                         |  |
| subjects affected / exposed                      | 21 / 280 (7.50%)        | 21 / 282 (7.45%)        |  |
| occurrences (all)                                | 27                      | 25                      |  |
| Peripheral sensory neuropathy                    |                         |                         |  |
| subjects affected / exposed                      | 25 / 280 (8.93%)        | 17 / 282 (6.03%)        |  |
| occurrences (all)                                | 32                      | 19                      |  |
| Blood and lymphatic system disorders             |                         |                         |  |

|  |                    |                    |  |
|--|--------------------|--------------------|--|
| Anaemia  |                    |                    |  |
| subjects affected / exposed                          | 137 / 280 (48.93%) | 85 / 282 (30.14%)  |  |
| occurrences (all)                                    | 253                | 182                |  |
| Febrile neutropenia                                  |                    |                    |  |
| subjects affected / exposed                          | 17 / 280 (6.07%)   | 7 / 282 (2.48%)    |  |
| occurrences (all)                                    | 21                 | 7                  |  |
| Leukopenia   |                    |                    |  |
| subjects affected / exposed                          | 126 / 280 (45.00%) | 105 / 282 (37.23%) |  |
| occurrences (all)                                    | 509                | 567                |  |
| Neutropenia  |                    |                    |  |
| subjects affected / exposed                          | 226 / 280 (80.71%) | 196 / 282 (69.50%) |  |
| occurrences (all)                                    | 1117               | 1127               |  |
| Thrombocytopenia                                     |                    |                    |  |
| subjects affected / exposed                          | 39 / 280 (13.93%)  | 6 / 282 (2.13%)    |  |
| occurrences (all)                                    | 89                 | 9                  |  |
| General disorders and administration site conditions |                    |                    |  |
| Asthenia   |                    |                    |  |
| subjects affected / exposed                          | 74 / 280 (26.43%)  | 57 / 282 (20.21%)  |  |
| occurrences (all)                                    | 166                | 100                |  |
| Chills   |                    |                    |  |
| subjects affected / exposed                          | 18 / 280 (6.43%)   | 18 / 282 (6.38%)   |  |
| occurrences (all)                                    | 22                 | 22                 |  |
| Fatigue  |                    |                    |  |
| subjects affected / exposed                          | 124 / 280 (44.29%) | 119 / 282 (42.20%) |  |
| occurrences (all)                                    | 252                | 217                |  |
| Oedema peripheral                                    |                    |                    |  |
| subjects affected / exposed                          | 39 / 280 (13.93%)  | 23 / 282 (8.16%)   |  |
| occurrences (all)                                    | 56                 | 25                 |  |
| Non-cardiac chest pain                               |                    |                    |  |
| subjects affected / exposed                          | 11 / 280 (3.93%)   | 20 / 282 (7.09%)   |  |
| occurrences (all)                                    | 13                 | 25                 |  |
| Pyrexia  |                    |                    |  |
| subjects affected / exposed                          | 107 / 280 (38.21%) | 65 / 282 (23.05%)  |  |
| occurrences (all)                                    | 181                | 128                |  |
| Pain   |                    |                    |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 20 / 280 (7.14%)<br>24 | 20 / 282 (7.09%)<br>27 |  |
| Gastrointestinal disorders                       |                        |                        |  |
| Abdominal pain                                   |                        |                        |  |
| subjects affected / exposed                      | 45 / 280 (16.07%)      | 52 / 282 (18.44%)      |  |
| occurrences (all)                                | 63                     | 69                     |  |
| Abdominal pain upper                             |                        |                        |  |
| subjects affected / exposed                      | 34 / 280 (12.14%)      | 40 / 282 (14.18%)      |  |
| occurrences (all)                                | 48                     | 54                     |  |
| Constipation                                     |                        |                        |  |
| subjects affected / exposed                      | 84 / 280 (30.00%)      | 88 / 282 (31.21%)      |  |
| occurrences (all)                                | 99                     | 121                    |  |
| Diarrhoea  |                        |                        |  |
| subjects affected / exposed                      | 108 / 280 (38.57%)     | 88 / 282 (31.21%)      |  |
| occurrences (all)                                | 200                    | 177                    |  |
| Dry mouth  |                        |                        |  |
| subjects affected / exposed                      | 14 / 280 (5.00%)       | 7 / 282 (2.48%)        |  |
| occurrences (all)                                | 16                     | 10                     |  |
| Dyspepsia  |                        |                        |  |
| subjects affected / exposed                      | 21 / 280 (7.50%)       | 25 / 282 (8.87%)       |  |
| occurrences (all)                                | 28                     | 33                     |  |
| Mouth ulceration                                 |                        |                        |  |
| subjects affected / exposed                      | 32 / 280 (11.43%)      | 6 / 282 (2.13%)        |  |
| occurrences (all)                                | 68                     | 8                      |  |
| Nausea   |                        |                        |  |
| subjects affected / exposed                      | 98 / 280 (35.00%)      | 105 / 282 (37.23%)     |  |
| occurrences (all)                                | 151                    | 163                    |  |
| Stomatitis                                       |                        |                        |  |
| subjects affected / exposed                      | 174 / 280 (62.14%)     | 78 / 282 (27.66%)      |  |
| occurrences (all)                                | 412                    | 140                    |  |
| Vomiting   |                        |                        |  |
| subjects affected / exposed                      | 57 / 280 (20.36%)      | 59 / 282 (20.92%)      |  |
| occurrences (all)                                | 88                     | 106                    |  |
| Respiratory, thoracic and mediastinal disorders  |                        |                        |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Cough   |                   |                   |  |
| subjects affected / exposed                     | 84 / 280 (30.00%) | 55 / 282 (19.50%) |  |
| occurrences (all)                               | 102               | 70                |  |
| Dyspnoea  |                   |                   |  |
| subjects affected / exposed                     | 51 / 280 (18.21%) | 40 / 282 (14.18%) |  |
| occurrences (all)                               | 63                | 50                |  |
| Epistaxis                                       |                   |                   |  |
| subjects affected / exposed                     | 64 / 280 (22.86%) | 38 / 282 (13.48%) |  |
| occurrences (all)                               | 90                | 51                |  |
| Oropharyngeal pain                              |                   |                   |  |
| subjects affected / exposed                     | 27 / 280 (9.64%)  | 27 / 282 (9.57%)  |  |
| occurrences (all)                               | 32                | 33                |  |
| Pneumonitis                                     |                   |                   |  |
| subjects affected / exposed                     | 17 / 280 (6.07%)  | 9 / 282 (3.19%)   |  |
| occurrences (all)                               | 19                | 9                 |  |
| Rhinorrhoea                                     |                   |                   |  |
| subjects affected / exposed                     | 17 / 280 (6.07%)  | 14 / 282 (4.96%)  |  |
| occurrences (all)                               | 21                | 17                |  |
| Skin and subcutaneous tissue disorders          |                   |                   |  |
| Rash  |                   |                   |  |
| subjects affected / exposed                     | 71 / 280 (25.36%) | 54 / 282 (19.15%) |  |
| occurrences (all)                               | 105               | 81                |  |
| Pruritus  |                   |                   |  |
| subjects affected / exposed                     | 16 / 280 (5.71%)  | 29 / 282 (10.28%) |  |
| occurrences (all)                               | 30                | 38                |  |
| Alopecia  |                   |                   |  |
| subjects affected / exposed                     | 22 / 280 (7.86%)  | 29 / 282 (10.28%) |  |
| occurrences (all)                               | 24                | 29                |  |
| Psychiatric disorders                           |                   |                   |  |
| Anxiety   |                   |                   |  |
| subjects affected / exposed                     | 13 / 280 (4.64%)  | 18 / 282 (6.38%)  |  |
| occurrences (all)                               | 14                | 18                |  |
| Insomnia  |                   |                   |  |
| subjects affected / exposed                     | 34 / 280 (12.14%) | 27 / 282 (9.57%)  |  |
| occurrences (all)                               | 39                | 31                |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |

|                                    |                   |                   |  |
|------------------------------------|-------------------|-------------------|--|
| Back pain                          |                   |                   |  |
| subjects affected / exposed        | 37 / 280 (13.21%) | 46 / 282 (16.31%) |  |
| occurrences (all)                  | 52                | 59                |  |
| Arthralgia                         |                   |                   |  |
| subjects affected / exposed        | 48 / 280 (17.14%) | 36 / 282 (12.77%) |  |
| occurrences (all)                  | 64                | 44                |  |
| Bone pain                          |                   |                   |  |
| subjects affected / exposed        | 28 / 280 (10.00%) | 24 / 282 (8.51%)  |  |
| occurrences (all)                  | 33                | 32                |  |
| Muscle spasms                      |                   |                   |  |
| subjects affected / exposed        | 31 / 280 (11.07%) | 47 / 282 (16.67%) |  |
| occurrences (all)                  | 45                | 69                |  |
| Musculoskeletal chest pain         |                   |                   |  |
| subjects affected / exposed        | 16 / 280 (5.71%)  | 12 / 282 (4.26%)  |  |
| occurrences (all)                  | 18                | 13                |  |
| Musculoskeletal pain               |                   |                   |  |
| subjects affected / exposed        | 14 / 280 (5.00%)  | 14 / 282 (4.96%)  |  |
| occurrences (all)                  | 15                | 15                |  |
| Myalgia                            |                   |                   |  |
| subjects affected / exposed        | 39 / 280 (13.93%) | 31 / 282 (10.99%) |  |
| occurrences (all)                  | 51                | 42                |  |
| Pain in extremity                  |                   |                   |  |
| subjects affected / exposed        | 42 / 280 (15.00%) | 44 / 282 (15.60%) |  |
| occurrences (all)                  | 51                | 59                |  |
| Infections and infestations        |                   |                   |  |
| Nasopharyngitis                    |                   |                   |  |
| subjects affected / exposed        | 37 / 280 (13.21%) | 29 / 282 (10.28%) |  |
| occurrences (all)                  | 67                | 62                |  |
| Upper respiratory tract infection  |                   |                   |  |
| subjects affected / exposed        | 38 / 280 (13.57%) | 26 / 282 (9.22%)  |  |
| occurrences (all)                  | 55                | 36                |  |
| Urinary tract infection            |                   |                   |  |
| subjects affected / exposed        | 26 / 280 (9.29%)  | 18 / 282 (6.38%)  |  |
| occurrences (all)                  | 37                | 27                |  |
| Metabolism and nutrition disorders |                   |                   |  |

|   |                          |                         |  |
|---|--------------------------|-------------------------|--|
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)    | 94 / 280 (33.57%)<br>131 | 49 / 282 (17.38%)<br>60 |  |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all) | 26 / 280 (9.29%)<br>30   | 12 / 282 (4.26%)<br>36  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)        | 26 / 280 (9.29%)<br>37   | 15 / 282 (5.32%)<br>22  |  |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all) | 23 / 280 (8.21%)<br>36   | 9 / 282 (3.19%)<br>10   |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)          | 34 / 280 (12.14%)<br>62  | 19 / 282 (6.74%)<br>24  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 15 March 2010   | Amendment 1 introduced the following non-administrative changes and was issued when 16 patients had been randomized: Guidelines regarding the management of HBV and HCV infections were added. Reactivation of HBV has been observed in cancer patients receiving either chemotherapy or   |
| 25 January 2011 | Amendment 2 was issued when 163 patients had been randomized. The primary purpose of this amendment was to revise exclusion criterion number 4, which had originally excluded all patients with a history of CNS metastases. The amended criterion allowed patients with previously treated CNS metastases to enroll in the study provided that the last treatment received for the CNS metastases was at least 8 weeks prior to randomization, including radiotherapy, steroids and anti-epileptic medication. A total of nine patients with CNS metastases were enrolled in this trial and the time to progression results suggested that everolimus can positively affect CNS disease. Accordingly, |
| 15 May 2013     | The key changes for Amendment 3 included the following: conduct and dissemination of OS analyses results to Novartis personnel and health authorities; inclusion of central review for tumor assessment data. Overall survival (OS) is pre-specified as a key secondary endpoint, as per the original protocol, results of OS analysis were not to be communicated to clinical team or any party   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

cut off date for the Safety data: 1 Apr 2015

Notes: