



## Clinical trial results:

### A Randomized, Multicenter, Open-Label, Two-Arm, Phase III Neoadjuvant Study Evaluating Trastuzumab Emtansine Plus Pertuzumab Compared with Chemotherapy Plus Trastuzumab and Pertuzumab for Patients with HER2-Positive Breast Cancer

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-004879-38 |
| Trial protocol           | BE ES DE FR IE |
| Global end of trial date | 29 May 2018    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 14 June 2019     |
| First version publication date | 19 December 2016 |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BO28408 |
|-----------------------|---------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Hoffmann-La Roche  |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH4070  |
| Public contact               | Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       |    |
| 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                       | 29 May 2018 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 29 May 2018 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

A Study Evaluating Trastuzumab Emtansine Plus Pertuzumab Compared With Chemotherapy Plus Trastuzumab and Pertuzumab for Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 25 June 2014 |
| 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 | Canada: 25             |
| Country: Number of subjects enrolled | United States: 83      |
| Country: Number of subjects enrolled | Korea, Republic of: 59 |
| Country: Number of subjects enrolled | Russian Federation: 61 |
| Country: Number of subjects enrolled | France: 27             |
| Country: Number of subjects enrolled | Taiwan: 42             |
| Country: Number of subjects enrolled | Ukraine: 5             |
| Country: Number of subjects enrolled | Belgium: 30            |
| Country: Number of subjects enrolled | Germany: 24            |
| Country: Number of subjects enrolled | Spain: 88              |
| Worldwide total number of subjects   | 444                    |
| EEA total number of subjects         | 169                    |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|  |     |
|--|-----|
| Infants and toddlers (28 days-23 months) | 0   |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 398 |
| From 65 to 84 years                      | 46  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 574 participants were screened at 65 sites in 10 countries, of which 444 participants were randomized in two arms: Trastuzumab (TCH) + Pertuzumab (P) (Arm A) and Trastuzumab Emtansine (TDM1) + P (Arm B)

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| Arm title                    | TCH + P |

Arm description:

Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m<sup>2</sup>) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter\* minute (mg/mL\*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).

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

Dosage and administration details:

Carboplatin IV infusion at a dose to achieve an AUC of 6 mg\*min/mL q3w

|  |   |
|--|---|
| Investigational medicinal product name | Pertuzumab  |
| Investigational medicinal product code |   |
| Other name                             | Perjeta®, RO4368451   |
| Pharmaceutical forms                   | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Pertuzumab 840 mg (loading dose); and 420 mg (maintenance dose) IV infusion q3w

|  |   |
|--|---|
| Investigational medicinal product name | Trastuzumab   |
| Investigational medicinal product code |   |
| Other name                             | Herceptin®  |
| Pharmaceutical forms                   | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Trastuzumab 8 mg/kg (loading dose); and 6 mg/kg (maintenance dose) IV infusion q3w

|  |   |
|--|---|
| Investigational medicinal product name | Docetaxel   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Docetaxel 75 mg/m<sup>2</sup> IV infusion q3w

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | T-DM1 + P |
|------------------|-----------|

Arm description:

Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Trastuzumab Emtansine   |
| Investigational medicinal product code |   |
| Other name                             | Kadcyla®, RO5304020   |
| Pharmaceutical forms                   | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Trastuzumab Emtansine 3.6 mg/kg IV infusion q3w

|  |   |
|--|---|
| Investigational medicinal product name | Pertuzumab  |
| Investigational medicinal product code |   |
| Other name                             | Perjeta®, RO4368451   |
| Pharmaceutical forms                   | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Pertuzumab 840 mg (loading dose); and 420 mg (maintenance dose) IV infusion q3w

| <b>Number of subjects in period 1</b> | TCH + P | T-DM1 + P |
|---------------------------------------|---------|-----------|
| Started                               | 221     | 223       |
| Completed                             | 196     | 189       |
| Not completed                         | 25      | 34        |
| Adverse event, serious fatal          | 5       | 6         |
| Consent withdrawn by subject          | 14      | 18        |
| Unspecified                           | 2       | 2         |
| Lost to follow-up                     | 4       | 8         |

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | TCH + P |
|-----------------------|---------|

Reporting group description:

Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m<sup>2</sup>) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter\* minute (mg/mL\*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).

|                       |           |
|-----------------------|-----------|
| Reporting group title | T-DM1 + P |
|-----------------------|-----------|

Reporting group description:

Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).

| Reporting group values                                | TCH + P | T-DM1 + P | Total |
|---|---------|-----------|-------|
| Number of subjects                                    | 221     | 223       | 444   |
| 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)                                  | 200     | 198       | 398   |
| From 65-84 years                                      | 21      | 25        | 46    |
| 85 years and over                                     | 0       | 0         | 0     |
| Age Continuous<br>Units: years                        |         |           |       |
| arithmetic mean                                       | 49.3    | 50.5      |       |
| standard deviation                                    | ± 11.2  | ± 10.6    | -     |
| Sex: Female, Male<br>Units: Subjects                  |         |           |       |
| Female  | 221     | 222       | 443   |
| Male  | 0       | 1         | 1     |

## End points

### End points reporting groups

|  |           |
|--|-----------|
| Reporting group title  | TCH + P   |
| Reporting group description:<br>Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m <sup>2</sup> ) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter* minute (mg/mL*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles). |           |
| Reporting group title  | T-DM1 + P |
| Reporting group description:<br>Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).   |           |

### Primary: Percentage of Subjects With Total Pathological Complete Response (tpCR) Assessed Based on Tumor Samples

|  |   |
|--|---|
| End point title  | Percentage of Subjects With Total Pathological Complete Response (tpCR) Assessed Based on Tumor Samples |
| End point description:<br>tpCR was assessed by local pathology review on samples taken at surgery following completion of neoadjuvant therapy. tpCR was defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes ( that is [i.e.], ypT0/is, ypN0 in the American Joint Committee on Cancer [AJCC] staging system, 7th edition). Percentage of subjects with tpCR was reported. |   |
| End point type   | Primary   |
| End point timeframe:<br>Pre-surgery (within 6 weeks after neoadjuvant therapy; up to approximately 6 months)   |   |

| End point values                 | TCH + P               | T-DM1 + P             |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 221                   | 223                   |  |  |
| Units: Percentage of Subjects    |                       |                       |  |  |
| number (confidence interval 95%) | 56.1 (49.29 to 62.76) | 44.4 (37.76 to 51.18) |  |  |

### Statistical analyses

|  |                     |
|--|---------------------|
| Statistical analysis title   | tpCR Analysis       |
| Statistical analysis description:<br>95% CI for the difference in tPCR rates between treatment arms was calculated using normal approximation. |                     |
| Comparison groups  | TCH + P v T-DM1 + P |

|   |                                    |
|---|------------------------------------|
| Number of subjects included in analysis | 444                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           |                                    |
| P-value                                 | = 0.0126 <sup>[1]</sup>            |
| Method                                  | Cochran-Mantel-Haenszel Chi-Square |
| Parameter estimate                      | Difference in tpCR rate            |
| Point estimate                          | -11.71                             |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -20.95                             |
| upper limit                             | -2.48                              |

Notes:

[1] - Threshold for significance at 5%

## Secondary: Percentage of Subjects Who Received Breast-Conserving Surgery (BCS)

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Received Breast-Conserving Surgery (BCS) |
|-----------------|---|

End point description:

BCS rate was defined as the percentage of subjects who achieve BCS out of the ITT population of subjects without inflammatory breast cancer.

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

End point timeframe:

Surgery performed after completion of neoadjuvant therapy (approximately 6 months after neoadjuvant period)

| End point values                 | TCH + P               | T-DM1 + P             |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 213                   | 218                   |  |  |
| Units: Percentage of Subjects    |                       |                       |  |  |
| number (confidence interval 95%) | 52.6 (45.65 to 59.45) | 41.7 (35.12 to 48.33) |  |  |

## Statistical analyses

|                            |              |
|----------------------------|--------------|
| Statistical analysis title | BCS Analysis |
|----------------------------|--------------|

Statistical analysis description:

95% CI for the difference in BCS rate between treatment arms was calculated using normal approximation.

|   |   |
|---|---|
| Comparison groups                       | T-DM1 + P v TCH + P                     |
| Number of subjects included in analysis | 431                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           |   |
| P-value                                 | = 0.0228                                |
| Method                                  | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate                      | Difference in BCS rate                  |
| Point estimate                          | -10.84                                  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -20.21  |
| upper limit         | -1.47   |

### Secondary: Percentage of Subjects With Selected Adverse Events (AEs)

|   |   |
|---|---|
| End point title   | Percentage of Subjects With Selected Adverse Events (AEs) |
| End point description:<br>Selected AEs included hepatotoxicity, pulmonary toxicity, cardiac dysfunction, neutropenia, thrombocytopenia, peripheral neuropathy, hemorrhage, infusion related reaction (IRR)/hypersensitivity, IRR/Hypersensitivity symptoms, rash, diarrhea and mucositis. An AE was defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline to end of study (approximately 47 months)  |   |

| End point values              | TCH + P         | T-DM1 + P       |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 219             | 223             |  |  |
| Units: Percentage of Subjects |                 |                 |  |  |
| number (not applicable)       |                 |                 |  |  |
| Hepatotoxicity                | 14.2            | 39.0            |  |  |
| Pulmonary Toxicity            | 0.9             | 4.9             |  |  |
| Cardiac Dysfunction           | 4.6             | 1.3             |  |  |
| Neutropenia                   | 39.7            | 8.1             |  |  |
| Thrombocytopenia              | 22.8            | 17.9            |  |  |
| Peripheral Neuropathy         | 47.5            | 28.7            |  |  |
| Hemorrhage                    | 19.2            | 33.2            |  |  |
| IRR/Hypersensitivity          | 13.7            | 22.9            |  |  |
| IRR/Hypersensitivity symptoms | 7.8             | 19.3            |  |  |
| Rash                          | 44.7            | 36.8            |  |  |
| Diarrhea                      | 76.7            | 38.6            |  |  |
| Mucositis                     | 43.8            | 24.7            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects by Response for Neuropathy Single Item

|   |   |
|---|---|
| End point title   | Percentage of Subjects by Response for Neuropathy Single Item |
| End point description:<br>Subjects answered the question "Did you have tingling hands/feet?", from the Modified Quality of Life |   |

Questionnaire Breast Cancer 23 (mQLQ-BR23), on a 5-point scale (1 'Not at all', 2 'A little', 3 'Somewhat', 4 'Quite a bit', 5 'Very much'). Percentage of subjects by each response was reported.

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

End point timeframe:

Baseline,Cycle(C) 3,C5 of neoadjuvant period (each C=21 days); pre-surgery visit (within 6weeks after neoadjuvant therapy; up to approx 6months), C4 & 8 of Adjuvant Period (each C=21 days), End of Treatment, Follow up 2 & 4 (approx 47 months)

| End point values                  | TCH + P         | T-DM1 + P       |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 194             | 205             |  |  |
| Units: Percentage of Subjects     |                 |                 |  |  |
| number (not applicable)           |                 |                 |  |  |
| Not at all: Baseline              | 78.7            | 81.2            |  |  |
| A little bit: Baseline            | 9.5             | 9.4             |  |  |
| Somewhat: Baseline                | 0               | 0               |  |  |
| Quite a bit: Baseline             | 0.9             | 0.9             |  |  |
| Very much: Baseline               | 0.5             | 0               |  |  |
| Not at all: Neoadjuvant Cycle 3   | 54.3            | 59.6            |  |  |
| A little bit: Neoadjuvant Cycle 3 | 20.8            | 19.3            |  |  |
| Somewhat: Neoadjuvant Cycle 3     | 0               | 0               |  |  |
| Quite a bit: Neoadjuvant Cycle 3  | 3.2             | 2.7             |  |  |
| Very much: Neoadjuvant Cycle 3    | 1.8             | 0.4             |  |  |
| Not at all: Neoadjuvant Cycle 5   | 37.1            | 54.3            |  |  |
| A little bit: Neoadjuvant Cycle 5 | 29.9            | 21.1            |  |  |
| Somewhat: Neoadjuvant Cycle 5     | 0               | 0               |  |  |
| Quite a bit: Neoadjuvant Cycle 5  | 8.6             | 2.7             |  |  |
| Very much: Neoadjuvant Cycle 5    | 6.8             | 1.8             |  |  |
| Not at all: Pre-Surgery           | 22.6            | 52.0            |  |  |
| A little bit: Pre-Surgery         | 29.0            | 17.9            |  |  |
| Somewhat: Pre-Surgery             | 0               | 0               |  |  |
| Quite a bit: Pre-Surgery          | 15.4            | 5.4             |  |  |
| Very much: Pre-Surgery            | 10.0            | 1.3             |  |  |
| Not at all: Adjuvant Cycle 4      | 31.2            | 42.6            |  |  |
| A little bit: Adjuvant Cycle 4    | 31.7            | 15.2            |  |  |
| Somewhat: Adjuvant Cycle 4        | 0               | 0               |  |  |
| Quite a bit: Adjuvant Cycle 4     | 9.5             | 9               |  |  |
| Very much: Adjuvant Cycle 4       | 6.3             | 2.7             |  |  |
| Not at all: Adjuvant Cycle 8      | 33.0            | 31.8            |  |  |
| A little bit: Adjuvant Cycle 8    | 28.1            | 19.3            |  |  |
| Somewhat: Adjuvant Cycle 8        | 0               | 0               |  |  |
| Quite a bit: Adjuvant Cycle 8     | 10.9            | 9.0             |  |  |
| Very much: Adjuvant Cycle 8       | 4.1             | 4.0             |  |  |
| Not at all: End of Therapy        | 31.2            | 31.4            |  |  |
| A little bit: End of Therapy      | 30.8            | 23.8            |  |  |
| Somewhat: End of Therapy          | 0               | 0               |  |  |
| Quite a bit: End of Therapy       | 10.9            | 12.1            |  |  |
| Very much: End of Therapy         | 5.0             | 6.7             |  |  |
| Not at all: Follow-up 2           | 38.0            | 32.7            |  |  |

|                           |      |      |  |  |
|---------------------------|------|------|--|--|
| A little bit: Follow-up 2 | 19.9 | 19.3 |  |  |
| Somewhat: Follow-up 2     | 0    | 0    |  |  |
| Quite a bit: Follow-up 2  | 5.9  | 7.6  |  |  |
| Very much: Follow-up 2    | 4.1  | 1.3  |  |  |
| Not at all: Follow-up 4   | 39.8 | 32.7 |  |  |
| A little bit: Follow-up 4 | 15.4 | 17.9 |  |  |
| Somewhat: Follow-up 4     | 0    | 0    |  |  |
| Quite a bit: Follow-up 4  | 4.1  | 3.1  |  |  |
| Very much: Follow-up 4    | 2.3  | 1.8  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects by Response for Skin Problem Single Items

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects by Response for Skin Problem Single Items |
|-----------------|--|

End point description:

Subjects answered the Question 1 "Did itching skin bother you?" and Question 2 "Have you had skin problems?", from the mQLQ-BR23, on a 5-point scale (1 'Not at all', 2 'A little', 3 'Somewhat', 4 'Quite a bit', 5 'Very much'). Percentage of subjects by each response was reported.

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

End point timeframe:

Baseline, Cycle(C) 3, C5 of neoadjuvant period (each C=21 days); pre-surgery visit (within 6 weeks after neoadjuvant therapy; up to approx 6 months), C4 & 8 of Adjuvant Period (each C=21 days), End of Treatment, Follow up 2 & 4 (approx 47 months)

| End point values                      | TCH + P         | T-DM1 + P       |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 193             | 205             |  |  |
| Units: Percentage of Subjects         |                 |                 |  |  |
| number (not applicable)               |                 |                 |  |  |
| Q1: Not at all: Baseline              | 71.9            | 72.6            |  |  |
| Q1: A little bit: Baseline            | 14.9            | 16.1            |  |  |
| Q1: Somewhat: Baseline                | 0               | 0               |  |  |
| Q1: Quite a bit: Baseline             | 2.3             | 2.2             |  |  |
| Q1: Very much: Baseline               | 0               | 0.4             |  |  |
| Q1: Not at all: Neoadjuvant Cycle 3   | 35.3            | 48.9            |  |  |
| Q1: A little bit: Neoadjuvant Cycle 3 | 31.2            | 27.4            |  |  |
| Q1: Somewhat: Neoadjuvant Cycle 3     | 0               | 0               |  |  |
| Q1: Quite a bit: Neoadjuvant Cycle 3  | 10.9            | 4.0             |  |  |
| Q1: Very much: Neoadjuvant Cycle 3    | 2.3             | 1.8             |  |  |
| Q1: Not at all: Neoadjuvant Cycle 5   | 48.9            | 46.2            |  |  |
| Q1: A little bit: Neoadjuvant Cycle 5 | 23.1            | 26.0            |  |  |
| Q1: Somewhat: Neoadjuvant Cycle 5     | 0               | 0               |  |  |
| Q1: Quite a bit: Neoadjuvant Cycle 5  | 7.7             | 6.3             |  |  |
| Q1: Very much: Neoadjuvant Cycle 5    | 2.3             | 1.3             |  |  |

|                                       |      |      |  |  |
|---------------------------------------|------|------|--|--|
| Q1: Not at all: Pre-Surgery           | 40.3 | 48.0 |  |  |
| Q1: A little bit: Pre-Surgery         | 26.7 | 21.5 |  |  |
| Q1: Somewhat: Pre-Surgery             | 0    | 0    |  |  |
| Q1: Quite a bit: Pre-Surgery          | 7.2  | 5.8  |  |  |
| Q1: Very much: Pre-Surgery            | 2.7  | 1.3  |  |  |
| Q1: Not at all: Adjuvant Cycle 4      | 38.5 | 39.0 |  |  |
| Q1: A little bit: Adjuvant Cycle 4    | 23.5 | 21.5 |  |  |
| Q1: Somewhat: Adjuvant Cycle 4        | 0    | 0    |  |  |
| Q1: Quite a bit: Adjuvant Cycle 4     | 9.5  | 6.7  |  |  |
| Q1: Very much: Adjuvant Cycle 4       | 6.8  | 2.2  |  |  |
| Q1: Not at all: Adjuvant Cycle 8      | 34.8 | 39.0 |  |  |
| Q1: A little bit: Adjuvant Cycle 8    | 27.6 | 15.7 |  |  |
| Q1: Somewhat: Adjuvant Cycle 8        | 0    | 0    |  |  |
| Q1: Quite a bit: Adjuvant Cycle 8     | 9.0  | 6.3  |  |  |
| Q1: Very much: Adjuvant Cycle 8       | 4.1  | 3.1  |  |  |
| Q1: Not at all: End of Therapy        | 39.4 | 42.6 |  |  |
| Q1: A little bit: End of Therapy      | 26.7 | 22.9 |  |  |
| Q1: Somewhat: End of Therapy          | 0    | 0    |  |  |
| Q1: Quite a bit: End of Therapy       | 6.8  | 6.7  |  |  |
| Q1: Very much: End of Therapy         | 4.5  | 1.8  |  |  |
| Q1: Not at all: Follow-up 2           | 43.9 | 39.9 |  |  |
| Q1: A little bit: Follow-up 2         | 19.0 | 14.8 |  |  |
| Q1: Somewhat: Follow-up 2             | 0    | 0    |  |  |
| Q1: Quite a bit: Follow-up 2          | 3.6  | 4.0  |  |  |
| Q1: Very much: Follow-up 2            | 0.9  | 2.2  |  |  |
| Q1: Not at all: Follow-up 4           | 46.2 | 37.7 |  |  |
| Q1: A little bit: Follow-up 4         | 10.4 | 12.1 |  |  |
| Q1: Somewhat: Follow-up 4             | 0    | 0    |  |  |
| Q1: Quite a bit: Follow-up 4          | 3.2  | 4.5  |  |  |
| Q1: Very much: Follow-up 4            | 1.4  | 1.3  |  |  |
| Q2: Not at all: Baseline              | 64.7 | 67.3 |  |  |
| Q2: A little bit: Baseline            | 21.3 | 17.9 |  |  |
| Q2: Somewhat: Baseline                | 0    | 0    |  |  |
| Q2: Quite a bit: Baseline             | 3.2  | 5.8  |  |  |
| Q2: Very much: Baseline               | 0.5  | 0.4  |  |  |
| Q2: Not at all: Neoadjuvant Cycle 3   | 14.0 | 24.2 |  |  |
| Q2: A little bit: Neoadjuvant Cycle 3 | 40.7 | 38.6 |  |  |
| Q2: Somewhat: Neoadjuvant Cycle 3     | 0    | 0    |  |  |
| Q2: Quite a bit: Neoadjuvant Cycle 3  | 18.6 | 14.8 |  |  |
| Q2: Very much: Neoadjuvant Cycle 3    | 6.8  | 4.5  |  |  |
| Q2: Not at all: Neoadjuvant Cycle 5   | 21.3 | 25.6 |  |  |
| Q2: A little bit: Neoadjuvant Cycle 5 | 35.7 | 37.7 |  |  |
| Q2: Somewhat: Neoadjuvant Cycle 5     | 0    | 0    |  |  |
| Q2: Quite a bit: Neoadjuvant Cycle 5  | 20.4 | 12.6 |  |  |
| Q2: Very much: Neoadjuvant Cycle 5    | 5.0  | 4.0  |  |  |
| Q2: Not at all: Pre-Surgery           | 21.3 | 27.4 |  |  |
| Q2: A little bit: Pre-Surgery         | 33.9 | 37.2 |  |  |
| Q2: Somewhat: Pre-Surgery             | 0    | 0    |  |  |
| Q2: Quite a bit: Pre-Surgery          | 15.4 | 8.1  |  |  |
| Q2: Very much: Pre-Surgery            | 6.3  | 4.0  |  |  |
| Q2: Not at all: Adjuvant Cycle 4      | 23.5 | 24.2 |  |  |
| Q2: A little bit: Adjuvant Cycle 4    | 33.0 | 30.9 |  |  |

|                                    |      |      |  |  |
|------------------------------------|------|------|--|--|
| Q2: Somewhat: Adjuvant Cycle 4     | 0    | 0    |  |  |
| Q2: Quite a bit: Adjuvant Cycle 4  | 13.1 | 9.4  |  |  |
| Q2: Very much: Adjuvant Cycle 4    | 9.0  | 4.9  |  |  |
| Q2: Not at all: Adjuvant Cycle 8   | 23.1 | 25.6 |  |  |
| Q2: A little bit: Adjuvant Cycle 8 | 35.7 | 24.2 |  |  |
| Q2: Somewhat: Adjuvant Cycle 8     | 0    | 0    |  |  |
| Q2: Quite a bit: Adjuvant Cycle 8  | 12.2 | 9.9  |  |  |
| Q2: Very much: Adjuvant Cycle 8    | 5.0  | 4.5  |  |  |
| Q2: Not at all: End of Therapy     | 27.1 | 27.4 |  |  |
| Q2: A little bit: End of Therapy   | 33.9 | 30.9 |  |  |
| Q2: Somewhat: End of Therapy       | 0    | 0    |  |  |
| Q2: Quite a bit: End of Therapy    | 10.0 | 13.5 |  |  |
| Q2: Very much: End of Therapy      | 6.8  | 3.1  |  |  |
| Q2: Not at all: Follow-up 2        | 36.2 | 27.8 |  |  |
| Q2: A little bit: Follow-up 2      | 25.8 | 25.6 |  |  |
| Q2: Somewhat: Follow-up 2          | 0    | 0    |  |  |
| Q2: Quite a bit: Follow-up 2       | 4.1  | 6.3  |  |  |
| Q2: Very much: Follow-up 2         | 1.8  | 1.3  |  |  |
| Q2: Not at all: Follow-up 4        | 39.8 | 30.0 |  |  |
| Q2: A little bit: Follow-up 4      | 14.5 | 18.8 |  |  |
| Q2: Somewhat: Follow-up 4          | 0    | 0    |  |  |
| Q2: Quite a bit: Follow-up 4       | 4.5  | 4.5  |  |  |
| Q2: Very much: Follow-up 4         | 2.7  | 2.2  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects by Response for Hair Loss Single Item

| End point title  | Percentage of Subjects by Response for Hair Loss Single Item |
|--|--|
| End point description:   |  |
| Subjects answered the Question "Have you lost any hair?", from the mQLQ-BR23, on a 5-point scale (1 'Not at all', 2 'A little', 3 'Somewhat', 4 'Quite a bit', 5 'Very much'). Percentage of subjects by each response was reported.               |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline,Cycle(C) 3, C5 of neoadjuvant period (each C=21 days); pre-surgery visit (within 6weeks after neoadjuvant therapy; up to approx 6months), C4 & 8 of Adjuvant Period (each C=21 days), End of Treatment, Follow up 2 & 4(approx 47 months) |  |

| End point values              | TCH + P         | T-DM1 + P       |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 194             | 205             |  |  |
| Units: Percentage of Subjects |                 |                 |  |  |
| number (not applicable)       |                 |                 |  |  |
| Not at all: Baseline          | 81.4            | 87.4            |  |  |
| A little bit: Baseline        | 7.7             | 4.0             |  |  |

|                                   |      |      |  |  |
|-----------------------------------|------|------|--|--|
| Somewhat: Baseline                | 0    | 0    |  |  |
| Quite a bit: Baseline             | 0.5  | 0    |  |  |
| Very much: Baseline               | 0    | 0    |  |  |
| Not at all: Neoadjuvant Cycle 3   | 8.6  | 65.0 |  |  |
| A little bit: Neoadjuvant Cycle 3 | 11.3 | 16.6 |  |  |
| Somewhat: Neoadjuvant Cycle 3     | 0    | 0    |  |  |
| Quite a bit: Neoadjuvant Cycle 3  | 20.8 | 0.4  |  |  |
| Very much: Neoadjuvant Cycle 3    | 39.4 | 0    |  |  |
| Not at all: Neoadjuvant Cycle 5   | 20.4 | 58.7 |  |  |
| A little bit: Neoadjuvant Cycle 5 | 19.9 | 19.3 |  |  |
| Somewhat: Neoadjuvant Cycle 5     | 0    | 0    |  |  |
| Quite a bit: Neoadjuvant Cycle 5  | 15.8 | 1.3  |  |  |
| Very much: Neoadjuvant Cycle 5    | 26.2 | 0.4  |  |  |
| Not at all: Pre-Surgery           | 30.8 | 49.8 |  |  |
| A little bit: Pre-Surgery         | 13.6 | 24.7 |  |  |
| Somewhat: Pre-Surgery             | 0    | 0    |  |  |
| Quite a bit: Pre-Surgery          | 11.3 | 2.2  |  |  |
| Very much: Pre-Surgery            | 21.3 | 0    |  |  |
| Not at all: Adjuvant Cycle 4      | 67.9 | 50.2 |  |  |
| A little bit: Adjuvant Cycle 4    | 5.0  | 15.7 |  |  |
| Somewhat: Adjuvant Cycle 4        | 0    | 0    |  |  |
| Quite a bit: Adjuvant Cycle 4     | 3.2  | 2.2  |  |  |
| Very much: Adjuvant Cycle 4       | 2.7  | 1.3  |  |  |
| Not at all: Adjuvant Cycle 8      | 70.1 | 48.9 |  |  |
| A little bit: Adjuvant Cycle 8    | 4.1  | 14.3 |  |  |
| Somewhat: Adjuvant Cycle 8        | 0    | 0    |  |  |
| Quite a bit: Adjuvant Cycle 8     | 0.9  | 0.9  |  |  |
| Very much: Adjuvant Cycle 8       | 0.9  | 0    |  |  |
| Not at all: End of Therapy        | 69.7 | 57.8 |  |  |
| A little bit: End of Therapy      | 5.4  | 14.8 |  |  |
| Somewhat: End of Therapy          | 0    | 0    |  |  |
| Quite a bit: End of Therapy       | 0.9  | 0    |  |  |
| Very much: End of Therapy         | 1.8  | 1.3  |  |  |
| Not at all: Follow-up 2           | 55.7 | 48.4 |  |  |
| A little bit: Follow-up 2         | 9.0  | 11.7 |  |  |
| Somewhat: Follow-up 2             | 0    | 0    |  |  |
| Quite a bit: Follow-up 2          | 1.4  | 0.4  |  |  |
| Very much: Follow-up 2            | 1.8  | 0.4  |  |  |
| Not at all: Follow-up 4           | 52.9 | 41.3 |  |  |
| A little bit: Follow-up 4         | 7.2  | 11.2 |  |  |
| Somewhat: Follow-up 4             | 0    | 0    |  |  |
| Quite a bit: Follow-up 4          | 0    | 2.7  |  |  |
| Very much: Follow-up 4            | 1.4  | 0.4  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With a Clinically Meaningful Deterioration in

## Global Health Status (GHS)/Quality of Life (QoL) Score

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With a Clinically Meaningful Deterioration in Global Health Status (GHS)/Quality of Life (QoL) Score |
|-----------------|---|

End point description:

Subjects rated their quality of life (global health status) on European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ- C30), with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better quality of life. Clinically meaningful deterioration in GHS/QoL was defined as a decrease in score of 10 points in GHS/QoL.

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

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

| End point values              | TCH + P         | T-DM1 + P       |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 193             | 205             |  |  |
| Units: Percentage of Subjects |                 |                 |  |  |
| number (not applicable)       | 69.9            | 45.4            |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | GHS/QoL Score Analysis |
|----------------------------|------------------------|

Statistical analysis description:

95% CI for the difference in clinically meaningful deterioration in GHS/QoL score between treatment arms was calculated using normal approximation.

|   |                             |
|---|-----------------------------|
| Comparison groups                       | TCH + P v T-DM1 + P         |
| Number of subjects included in analysis | 398                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           |                             |
| Parameter estimate                      | Difference in Deterioration |
| Point estimate                          | -24.58                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -33.98                      |
| upper limit                             | -15.19                      |

## Secondary: Time to Clinically Meaningful Deterioration in GHS/QoL Score

|                 |  |
|-----------------|--|
| End point title | Time to Clinically Meaningful Deterioration in GHS/QoL Score |
|-----------------|--|

End point description:

Participants rated their quality of life (global health status) on EORTC QLQ C-30, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better quality of life. Time to deterioration was defined as the time from baseline to first 10-point (or greater) decrease as measured by GHS/QoL. All valid GHS/QoL questionnaires of the neoadjuvant phase including surgery were used. Participants without deterioration were censored at the time of completing the last GHS/QoL plus 1 day. Median time to deterioration was estimated with Kaplan-Meier method. The 95% confidence interval (CI) for the median was computed using the method of Brookmeyer and Crowley.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period |           |

| End point values                 | TCH + P             | T-DM1 + P           |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 191                 | 200                 |  |  |
| Units: months                    |                     |                     |  |  |
| median (confidence interval 95%) | 3.02 (2.83 to 3.38) | 4.63 (4.11 to 7.98) |  |  |

## Statistical analyses

| Statistical analysis title   | GHS/QoL Score Analysis |
|--|------------------------|
| Statistical analysis description:  |                        |
| Stratified cox proportional hazards regression model was used to estimate Hazard Ratio and CI. Stratification by hormonal receptor status and clinical stage at presentation (stratification factors). |                        |
| Comparison groups  | TCH + P v T-DM1 + P    |
| Number of subjects included in analysis  | 391                    |
| Analysis specification   | Pre-specified          |
| Analysis type  |                        |
| Parameter estimate   | Hazard ratio (HR)      |
| Point estimate   | 0.6                    |
| Confidence interval  |                        |
| level  | 95 %                   |
| sides  | 2-sided                |
| lower limit  | 0.46                   |
| upper limit  | 0.78                   |

## Secondary: Percentage of Subjects With a Clinically Meaningful Deterioration in Function Subscales

| End point title   | Percentage of Subjects With a Clinically Meaningful Deterioration in Function Subscales |
|---|---|
| End point description:  |   |
| Subjects rated their function on EORTC QLQ C-30, with total score and single-item (physical, cognitive and role functioning) scores ranging from 0 (worst) to 100 (best); where higher score indicates better functioning. Clinically meaningful deterioration was defined as a decrease in score of 10 points in physical function; decrease of 7 points in cognitive function and decrease of 14 points in role function. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period   |   |



| <b>End point values</b>       | TCH + P         | T-DM1 + P       |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 193             | 205             |  |  |
| Units: Percentage of Subjects |                 |                 |  |  |
| number (not applicable)       |                 |                 |  |  |
| Cognitive Functioning         | 59.1            | 42.4            |  |  |
| Physical Functioning          | 72.5            | 40.0            |  |  |
| Role Functioning              | 76.7            | 47.8            |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>  | Cognitive Functioning Analysis |
|--|--------------------------------|
| Statistical analysis description:  |                                |
| This is the statistical analysis for cognitive functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation. |                                |
| Comparison groups  | TCH + P v T-DM1 + P            |
| Number of subjects included in analysis  | 398                            |
| Analysis specification   | Pre-specified                  |
| Analysis type  |                                |
| Parameter estimate   | Difference in Deterioration    |
| Point estimate   | -16.63                         |
| Confidence interval  |                                |
| level  | 95 %                           |
| sides  | 2-sided                        |
| lower limit  | -26.32                         |
| upper limit  | -6.94                          |

| <b>Statistical analysis title</b>   | Role Functioning Analysis   |
|---|-----------------------------|
| Statistical analysis description:   |                             |
| This is the statistical analysis for role functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation. |                             |
| Comparison groups   | TCH + P v T-DM1 + P         |
| Number of subjects included in analysis   | 398                         |
| Analysis specification  | Pre-specified               |
| Analysis type   |                             |
| Parameter estimate  | Difference in Deterioration |
| Point estimate  | -28.88                      |
| Confidence interval   |                             |
| level   | 95 %                        |
| sides   | 2-sided                     |
| lower limit   | -37.95                      |
| upper limit   | -19.8                       |

| <b>Statistical analysis title</b> | Physical Functioning Analysis |
|-----------------------------------|-------------------------------|
|-----------------------------------|-------------------------------|

**Statistical analysis description:**

This is the statistical analysis for physical functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation.

|   |                             |
|---|-----------------------------|
| Comparison groups                       | TCH + P v T-DM1 + P         |
| Number of subjects included in analysis | 398                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           |                             |
| Parameter estimate                      | Difference in Deterioration |
| Point estimate                          | -32.54                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -41.74                      |
| upper limit                             | -23.34                      |

**Secondary: Time to Clinically Meaningful Deterioration in Function Subscale**

|                 |  |
|-----------------|--|
| End point title | Time to Clinically Meaningful Deterioration in Function Subscale |
|-----------------|--|

**End point description:**

Participants rated their function on EORTC QLQ C-30, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better functioning. Time to deterioration was defined as the time from baseline to first 10-point (or greater) decrease as measured by physical function; to first 14-point (or greater) decrease as measured by role function, to first 7-point (or greater) decrease as measured by cognitive function. Median time to deterioration was estimated with Kaplan-Meier method. The 95% CI for the median was computed using the method of Brookmeyer and Crowley. 9999 = not estimable value

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

**End point timeframe:**

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

| <b>End point values</b>          | TCH + P             | T-DM1 + P           |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 191                 | 200                 |  |  |
| Units: months                    |                     |                     |  |  |
| median (confidence interval 95%) |                     |                     |  |  |
| Physical Function                | 2.79 (2.79 to 2.96) | 4.86 (4.40 to 7.98) |  |  |
| Role Function                    | 2.79 (2.17 to 2.89) | 4.44 (4.04 to 4.53) |  |  |
| Cognitive Function               | 3.42 (3.02 to 4.24) | 4.44 (4.21 to 9999) |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of Subjects With a Clinically Meaningful Increase in**

## Symptom Subscales

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With a Clinically Meaningful Increase in Symptom Subscales |
|-----------------|---|

End point description:

Subjects rated their symptoms on EORTC QLQ C-30 and mQLQ-BR23, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates greater degree of symptoms. Clinically meaningful increase in symptoms was defined as an increase in score (deterioration) of 11 points in nausea and vomiting, pain, dyspnea; increase of 9 points in insomnia; increase of 14 points in appetite loss; increase of 15 points in diarrhea, constipation; increase of 10 points in fatigue, systemic therapy side effects, hair loss.

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

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

| End point values              | TCH + P         | T-DM1 + P       |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 194             | 205             |  |  |
| Units: Percentage of Subjects |                 |                 |  |  |
| number (not applicable)       |                 |                 |  |  |
| Appetite Loss                 | 61.1            | 47.8            |  |  |
| Any Hair Loss                 | 91.2            | 40.5            |  |  |
| Systemic Therapy Side-Effects | 89.7            | 75.1            |  |  |
| Constipation                  | 33.2            | 32.7            |  |  |
| Diarrhea                      | 79.3            | 50.7            |  |  |
| Dyspnea                       | 56.0            | 31.2            |  |  |
| Fatigue                       | 87.6            | 68.8            |  |  |
| Nausea/Vomiting               | 66.3            | 43.9            |  |  |
| Pain                          | 56.0            | 36.6            |  |  |
| Insomnia                      | 42.5            | 30.2            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Serum Concentration (Cmax) of Trastuzumab

|                 |   |
|-----------------|---|
| End point title | Maximum Observed Serum Concentration (Cmax) of Trastuzumab <sup>[2]</sup> |
|-----------------|---|

End point description:

Only participants who received trastuzumab were to be analyzed for this outcome.

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

End point timeframe:

15-30 minutes (min) post-study treatment infusion (infusion duration = 90 min) on Day 1 of Cycle 1 and 6 (each cycle = 21 days) in neoadjuvant and adjuvant period

Notes:

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

Justification: There was no statistics reported for this endpoint.

| End point values                          | TCH + P         |  |  |  |
|---|-----------------|--|--|--|
| Subject group type                        | Reporting group |  |  |  |
| Number of subjects analysed               | 214             |  |  |  |
| Units: micrograms per milliliter (mcg/mL) |                 |  |  |  |
| arithmetic mean (standard deviation)      |                 |  |  |  |
| Cycle 1 (neoadjuvant period)              | 167 (± 47.1)    |  |  |  |
| Cycle 6 (neoadjuvant period)              | 148 (± 44.7)    |  |  |  |
| Cycle 1 (adjuvant period)                 | 159 (± 36.2)    |  |  |  |
| Cycle 6 (adjuvant period)                 | 181 (± 30.7)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax of Trastuzumab Emtansine and Total Trastuzumab

|   |  |
|---|--|
| End point title   | Cmax of Trastuzumab Emtansine and Total Trastuzumab <sup>[3]</sup> |
| End point description:  |  |
| Only participants who received trastuzumab emtansine were to be analyzed for this outcome.  |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| 15-30 min post-study treatment infusion (infusion duration = 90 min) on Day 1 of Cycle 1 and 6 (each cycle = 21 days) in neoadjuvant and adjuvant period. |  |

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: There was no statistics reported for this endpoint.

| End point values                        | T-DM1 + P       |  |  |  |
|---|-----------------|--|--|--|
| Subject group type                      | Reporting group |  |  |  |
| Number of subjects analysed             | 222             |  |  |  |
| Units: mcg/mL                           |                 |  |  |  |
| arithmetic mean (standard deviation)    |                 |  |  |  |
| Trastuzumab emtansine: C1 (neoadjuvant) | 80.4 (± 26.5)   |  |  |  |
| Trastuzumab emtansine: C6 (neoadjuvant) | 71.7 (± 30.2)   |  |  |  |
| Total Trastuzumab: C1 (neoadjuvant)     | 79.1 (± 25.7)   |  |  |  |
| Total Trastuzumab: C6 (neoadjuvant)     | 79.1 (± 31.1)   |  |  |  |
| Trastuzumab emtansine: C1 (adjuvant)    | 70.4 (± 22.7)   |  |  |  |
| Trastuzumab emtansine: C6 (adjuvant)    | 73.1 (± 21.8)   |  |  |  |
| Total Trastuzumab: C1 (adjuvant)        | 73.0 (± 23.2)   |  |  |  |
| Total Trastuzumab: C6 (adjuvant)        | 82.6 (± 23.7)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Minimum Observed Serum Concentration (Cmin) of Trastuzumab**

|                 |   |
|-----------------|---|
| End point title | Minimum Observed Serum Concentration (Cmin) of Trastuzumab <sup>[4]</sup> |
|-----------------|---|

End point description:

Only participants who received trastuzumab were to be analyzed for this outcome.

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

End point timeframe:

Pre-study treatment infusion (0 hours [hr]) (infusion duration = 90 min) on Day 1 of Cycle 6 (cycle length = 21 days) in neoadjuvant and adjuvant period

Notes:

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

Justification: There was no statistics reported for this endpoint.

| End point values                     | TCH + P         |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 214             |  |  |  |
| Units: mcg/mL                        |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Trastuzumab (neoadjuvant period)     | 45.8 (± 17.8)   |  |  |  |
| Trastuzumab (adjuvant period)        | 21.8 (± 0.153)  |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Cmin of Trastuzumab Emtansine and Total Trastuzumab**

|                 |  |
|-----------------|--|
| End point title | Cmin of Trastuzumab Emtansine and Total Trastuzumab <sup>[5]</sup> |
|-----------------|--|

End point description:

Only participants who received trastuzumab emtansine were to be analyzed for this outcome.

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

End point timeframe:

Pre-study treatment infusion (0 hr) (infusion duration = 90 min) on Day 1 of Cycle 6 (cycle length = 21 days) in neoadjuvant and adjuvant period

Notes:

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

Justification: There was no statistics reported for this endpoint.

| End point values                     | T-DM1 + P       |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 222             |  |  |  |
| Units: mcg/mL                        |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Trastuzumab emtansine (neoadjuvant)  | 3.04 (± 7.43)   |  |  |  |
| Total Trastuzumab (neoadjuvant)      | 12.3 (± 8.68)   |  |  |  |
| Trastuzumab emtansine (adjuvant)     | 4.09 (± 11.7)   |  |  |  |
| Total Trastuzumab (adjuvant)         | 8.70 (± 6.98)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine (DM1) Concentrations

|                 |   |
|-----------------|---|
| End point title | Plasma N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine (DM1) Concentrations <sup>[6]</sup> |
|-----------------|---|

End point description:

DM1 is the metabolite of trastuzumab emtansine. Only participants who received trastuzumab emtansine were to be analyzed for this outcome.

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

End point timeframe:

15-30 min post-study treatment infusion (Cmax) on Day 1 of Cycle 1 and 6 in neoadjuvant and adjuvant period

Notes:

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

Justification: There was no statistics reported for this endpoint.

| End point values                        | T-DM1 + P       |  |  |  |
|---|-----------------|--|--|--|
| Subject group type                      | Reporting group |  |  |  |
| Number of subjects analysed             | 222             |  |  |  |
| Units: nanograms per milliliter (ng/mL) |                 |  |  |  |
| arithmetic mean (standard deviation)    |                 |  |  |  |
| C1: 15-30 min post-dose (neoadjuvant)   | 4.64 (± 2.33)   |  |  |  |
| C6: 15-30 min post-dose (neoadjuvant)   | 4.73 (± 2.61)   |  |  |  |
| C1: 15-30 min post-dose (adjuvant)      | 4.49 (± 2.33)   |  |  |  |
| C6: 15-30 min post-dose (adjuvant)      | 5.15 (± 8.28)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Serum Levels of Plasma DM1-Containing Catabolites Concentrations (in ng/mL) (Nonreducible Thioether Linker [MCC]-DM1 and Lysine [Lys]-MCC-DM1)

|                 |   |
|-----------------|---|
| End point title | Serum Levels of Plasma DM1-Containing Catabolites Concentrations (in ng/mL) (Nonreducible Thioether Linker [MCC]-DM1 and Lysine [Lys]-MCC-DM1) <sup>[7]</sup> |
|-----------------|---|

End point description:

9999 = not applicable

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

End point timeframe:

15-30 min post-study treatment infusion (Cmax) on Day 1 of Cycle 1 and 6 in neoadjuvant and adjuvant period

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: There was no statistics reported for this endpoint.

| End point values                     | T-DM1 + P       |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 222             |  |  |  |
| Units: ng/mL                         |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| C1: MCC-DM1 (Neoadjuvant Period)     | 8.18 (± 7.23)   |  |  |  |
| C1: Lys-MCC-DM1 (Neoadjuvant period) | 9999 (± 9999)   |  |  |  |
| C6: MCC-DM1 (Neoadjuvant Period)     | 8.22 (± 8.03)   |  |  |  |
| C6: Lys-MCC-DM1 (Neoadjuvant period) | 9999 (± 9999)   |  |  |  |
| C1: MCC-DM1 (Adjuvant Period)        | 7.98 (± 6.46)   |  |  |  |
| C1: Lys-MCC-DM1 (Adjuvant period)    | 9999 (± 9999)   |  |  |  |
| C6: MCC-DM1 (Adjuvant Period)        | 7.90 (± 5.37)   |  |  |  |
| C6: Lys-MCC-DM1 (Adjuvant period)    | 9999 (± 9999)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Anti-Therapeutic Antibodies (ATA) to TDM-1

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Anti-Therapeutic Antibodies (ATA) to TDM-1 <sup>[8]</sup> |
|-----------------|---|

End point description:

Subjects were considered post-baseline ATA positive if they had ATAs post-baseline that were either treatment-induced or treatment-enhanced. Subjects had treatment-induced ATAs if they had a negative or missing ATA result at baseline, and at least one positive ATA result post-baseline. Subjects had treatment-enhanced ATAs if they had a positive ATA result at baseline, and at least one positive ATA result post-baseline that was greater than or equal to ( $\geq$ ) 0.60 titer units higher than the result at baseline.

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

End point timeframe:

Baseline (b) (Pre-TDM1 [0 hr] infusion [infusion duration = 90 min] on Day 1 of Cycle 1); post-baseline (pb) (Pre-TDM1 infusion [0 hr] on Day 1 of Cycle 6) (each cycle = 21 days) in neoadjuvant and adjuvant period

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: There was no statistics reported for this endpoint.

| End point values                  | T-DM1 + P       |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 219             |  |  |  |
| Units: Percentage of Subjects     |                 |  |  |  |
| number (not applicable)           |                 |  |  |  |
| Neoadjuvant Phase (Baseline)      | 5.5             |  |  |  |
| Neoadjuvant Phase (Post-Baseline) | 7.5             |  |  |  |
| Adjuvant Phase (Baseline)         | 11.7            |  |  |  |

|                                |      |  |  |  |
|--------------------------------|------|--|--|--|
| Adjuvant Phase (Post-baseline) | 13.1 |  |  |  |
|--------------------------------|------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With ATA to Trastuzumab

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With ATA to Trastuzumab <sup>[9]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline (Pre-trastuzumab [0 hr] infusion [infusion duration = 90 min] on Day 1 of Cycle 1); post-baseline (Pre-trastuzumab infusion [0 hr] on Day 1 of Cycle 6) (each cycle = 21 days) in neoadjuvant and adjuvant period

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was no statistics reported for this endpoint.

| End point values                  | T-DM1 + P       |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 210             |  |  |  |
| Units: Percentage of Subjects     |                 |  |  |  |
| number (not applicable)           |                 |  |  |  |
| Neoadjuvant Phase (baseline)      | 11              |  |  |  |
| Neoadjuvant Phase (post-baseline) | 2.6             |  |  |  |
| Adjuvant Phase (baseline)         | 5.4             |  |  |  |
| Adjuvant Phase (post-baseline)    | 5.0             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

Overall survival in the overall study population was defined as the time from the date of randomization to the date of death from any cause. 3 years OS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after treatment.

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

End point timeframe:

From randomization until death or end of study period (up to approximately 47 months)



| <b>End point values</b>          | TCH + P             | T-DM1 + P           |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 221                 | 223                 |  |  |
| Units: Probability               |                     |                     |  |  |
| number (confidence interval 95%) | 97.6 (95.5 to 99.7) | 97.0 (94.6 to 99.4) |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Overall Survival    |
|---|---------------------|
| Comparison groups                       | TCH + P v T-DM1 + P |
| Number of subjects included in analysis | 444                 |
| Analysis specification                  | Pre-specified       |
| Analysis type                           |                     |
| P-value                                 | = 0.7557            |
| Method                                  | Logrank             |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 1.21                |
| Confidence interval                     |                     |
| level                                   | 95 %                |
| sides                                   | 2-sided             |
| lower limit                             | 0.37                |
| upper limit                             | 3.96                |

### Secondary: Event-free survival (EFS)

|  |                           |
|--|---------------------------|
| End point title  | Event-free survival (EFS) |
| End point description:   |                           |
| EFS is defined as the time from randomization to disease progression or disease recurrence (local, regional, distant, or contralateral, invasive or non-invasive), or death from any cause. 3 years EFS rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after treatment. |                           |
| End point type   | Secondary                 |
| End point timeframe:   |                           |
| From randomization up to disease progression or recurrence or death (up to approximately 47 months)  |                           |

| End point values                 | TCH + P                | T-DM1 + P              |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 221                    | 223                    |  |  |
| Units: Probability               |                        |                        |  |  |
| number (confidence interval 95%) | 94.21 (91.02 to 97.39) | 85.28 (80.47 to 90.08) |  |  |

## Statistical analyses

| Statistical analysis title              | Event-Free Survival Analysis |
|---|------------------------------|
| Comparison groups                       | TCH + P v T-DM1 + P          |
| Number of subjects included in analysis | 444                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           |                              |
| P-value                                 | = 0.0027                     |
| Method                                  | Logrank                      |
| Parameter estimate                      | Hazard ratio (HR)            |
| Point estimate                          | 2.61                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 1.36                         |
| upper limit                             | 4.98                         |

## Secondary: Invasive disease-free survival (IDFS)

|  |                                       |
|--|---------------------------------------|
| End point title  | Invasive disease-free survival (IDFS) |
| End point description:   |                                       |
| IDFS is defined only for participants who undergo surgery. IDFS is defined as the time from surgery to the first documented occurrence of an IDFS event, defined as: Ipsilateral invasive breast tumor recurrence; Ipsilateral local–regional invasive breast cancer recurrence; Distant recurrence; Contralateral invasive breast cancer; and death from any cause. 3 years of IDFS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after treatment. |                                       |
| End point type   | Secondary                             |
| End point timeframe:   |                                       |
| From surgery to the first documented occurrence of IDFC event (up to approximately 45 months)  |                                       |

| End point values                 | TCH + P                | T-DM1 + P              |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 214                    | 204                    |  |  |
| Units: Probability               |                        |                        |  |  |
| number (confidence interval 95%) | 91.99 (86.73 to 97.26) | 93.04 (89.39 to 96.69) |  |  |

## Statistical analyses

|   |                          |
|---|--------------------------|
| <b>Statistical analysis title</b>       | IDFS Event-Free Analysis |
| Comparison groups                       | TCH + P v T-DM1 + P      |
| Number of subjects included in analysis | 418                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| Parameter estimate                      | Hazard ratio (HR)        |
| Point estimate                          | 1.11                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.52                     |
| upper limit                             | 2.4                      |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

Adverse event reporting additional description:

Safety population was analyzed.

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

### Dictionary used

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

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

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | TCH + P |
|-----------------------|---------|

Reporting group description:

Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m<sup>2</sup>) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter\* minute (mg/mL\*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).

|                       |           |
|-----------------------|-----------|
| Reporting group title | T-DM1 + P |
|-----------------------|-----------|

Reporting group description:

Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).

| Serious adverse events  | TCH + P           | T-DM1 + P         |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed   | 71 / 219 (32.42%) | 30 / 223 (13.45%) |  |
| number of deaths (all causes)                                       | 5                 | 6                 |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Intraductal proliferative breast lesion                             |                   |                   |  |
| subjects affected / exposed   | 0 / 219 (0.00%)   | 1 / 223 (0.45%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Cervix carcinoma  |                   |                   |  |
| subjects affected / exposed   | 0 / 219 (0.00%)   | 1 / 223 (0.45%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Neuroendocrine tumour   |                   |                   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Uterine leiomyoma                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 219 (0.46%) | 0 / 223 (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                          | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypertensive crisis                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Shock haemorrhagic                                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pyrexia  |                 |                 |  |
| subjects affected / exposed                          | 2 / 219 (0.91%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Device related thrombosis                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Anaphylactic reaction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypersensitivity                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (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        |                 |                 |  |
| Adenomyosis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast haematoma                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 219 (0.00%) | 2 / 223 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchiectasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Anxiety   |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Lipase increased                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutrophil count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 219 (1.37%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| complications                                   |                 |                 |  |
| Subcutaneous haematoma                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural intestinal perforation               |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seroma  |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 219 (0.91%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus tachycardia                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 219 (0.91%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathy peripheral                           |                 |                 |  |



|   |                   |                 |  |
|---|-------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 219 (0.00%)   | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Seizure   |                   |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%)   | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Transient ischaemic attack                      |                   |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%)   | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Blood and lymphatic system disorders            |                   |                 |  |
| Anaemia   |                   |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%)   | 3 / 223 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Febrile neutropenia                             |                   |                 |  |
| subjects affected / exposed                     | 26 / 219 (11.87%) | 3 / 223 (1.35%) |  |
| occurrences causally related to treatment / all | 33 / 33           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Neutropenia                                     |                   |                 |  |
| subjects affected / exposed                     | 7 / 219 (3.20%)   | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 7 / 7             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Thrombocytopenia                                |                   |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%)   | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Gastrointestinal disorders                      |                   |                 |  |
| Abdominal pain                                  |                   |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%)   | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Abdominal pain upper                            |                   |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis   |                 |                 |  |
| subjects affected / exposed                     | 3 / 219 (1.37%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 9 / 219 (4.11%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 9 / 9           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (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                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 4 / 219 (1.83%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Nodular regenerative hyperplasia                |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bacteraemia                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cellulitis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 219 (0.91%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (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                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea infectious                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis infectious                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (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                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis norovirus                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Kidney infection                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 219 (0.91%) | 2 / 223 (0.90%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 2 / 219 (0.91%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin infection                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 3 / 223 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast abscess                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 219 (0.00%) | 1 / 223 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypermagnesaemia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 219 (0.46%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypomagnesaemia                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 219 (0.91%) | 0 / 223 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| Non-serious adverse events                            | TCH + P            | T-DM1 + P          |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 215 / 219 (98.17%) | 198 / 223 (88.79%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hot flush   |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 45 / 219 (20.55%)  | 22 / 223 (9.87%)   |  |
| occurrences (all)                                     | 47                 | 25                 |  |
| Hypertension  |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 15 / 219 (6.85%)   | 14 / 223 (6.28%)   |  |
| occurrences (all)                                     | 18                 | 14                 |  |
| General disorders and administration site conditions  |                    |                    |  |
| Asthenia  |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 61 / 219 (27.85%)  | 42 / 223 (18.83%)  |  |
| occurrences (all)                                     | 115                | 73                 |  |
| Chills  |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 9 / 219 (4.11%)    | 27 / 223 (12.11%)  |  |
| occurrences (all)                                     | 9                  | 32                 |  |
| Fatigue   |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 95 / 219 (43.38%)  | 83 / 223 (37.22%)  |  |
| occurrences (all)                                     | 143                | 116                |  |
| Influenza like illness                                |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 10 / 219 (4.57%)   | 16 / 223 (7.17%)   |  |
| occurrences (all)                                     | 12                 | 21                 |  |
| Mucosal inflammation                                  |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 30 / 219 (13.70%)  | 22 / 223 (9.87%)   |  |
| occurrences (all)                                     | 37                 | 29                 |  |
| Oedema peripheral                                     |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |

|  |  |   |  |
|--|--|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>31 / 219 (14.16%)</p> <p>38</p> <p>34 / 219 (15.53%)</p> <p>43</p>  | <p>10 / 223 (4.48%)</p> <p>11</p> <p>38 / 223 (17.04%)</p> <p>53</p>  |  |
| <p>Immune system disorders</p> <p>Hypersensitivity</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>11 / 219 (5.02%)</p> <p>17</p>  | <p>6 / 223 (2.69%)</p> <p>8</p>   |  |
| <p>Reproductive system and breast disorders</p> <p>Breast pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>12 / 219 (5.48%)</p> <p>13</p>  | <p>17 / 223 (7.62%)</p> <p>18</p>   |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rhinorrhoea</p> <p>alternative assessment type: Non-</p> | <p>21 / 219 (9.59%)</p> <p>26</p> <p>18 / 219 (8.22%)</p> <p>21</p> <p>24 / 219 (10.96%)</p> <p>31</p> <p>11 / 219 (5.02%)</p> <p>17</p> | <p>30 / 223 (13.45%)</p> <p>38</p> <p>18 / 223 (8.07%)</p> <p>22</p> <p>49 / 223 (21.97%)</p> <p>82</p> <p>10 / 223 (4.48%)</p> <p>11</p> |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| systematic                                  |                   |                   |  |
| subjects affected / exposed                 | 12 / 219 (5.48%)  | 11 / 223 (4.93%)  |  |
| occurrences (all)                           | 16                | 14                |  |
| Psychiatric disorders                       |                   |                   |  |
| Depression                                  |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 16 / 219 (7.31%)  | 10 / 223 (4.48%)  |  |
| occurrences (all)                           | 17                | 10                |  |
| Insomnia                                    |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 31 / 219 (14.16%) | 36 / 223 (16.14%) |  |
| occurrences (all)                           | 37                | 40                |  |
| Anxiety                                     |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 14 / 219 (6.39%)  | 13 / 223 (5.83%)  |  |
| occurrences (all)                           | 15                | 15                |  |
| Investigations                              |                   |                   |  |
| Alanine aminotransferase increased          |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 24 / 219 (10.96%) | 64 / 223 (28.70%) |  |
| occurrences (all)                           | 37                | 83                |  |
| Aspartate aminotransferase increased        |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 21 / 219 (9.59%)  | 55 / 223 (24.66%) |  |
| occurrences (all)                           | 37                | 74                |  |
| Neutrophil count decreased                  |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 22 / 219 (10.05%) | 5 / 223 (2.24%)   |  |
| occurrences (all)                           | 44                | 6                 |  |
| Platelet count decreased                    |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 26 / 219 (11.87%) | 23 / 223 (10.31%) |  |
| occurrences (all)                           | 37                | 38                |  |
| Weight decreased                            |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |

|  |  |   |  |
|--|--|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood bilirubin increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>24 / 219 (10.96%)</p> <p>24</p> <p>17 / 219 (7.76%)</p> <p>22</p> <p>1 / 219 (0.46%)</p> <p>3</p>                                       | <p>18 / 223 (8.07%)</p> <p>19</p> <p>8 / 223 (3.59%)</p> <p>11</p> <p>20 / 223 (8.97%)</p> <p>28</p>                                    |  |
| <p>Injury, poisoning and procedural complications</p> <p>Radiation skin injury</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>46 / 219 (21.00%)</p> <p>48</p>   | <p>21 / 223 (9.42%)</p> <p>22</p>   |  |
| <p>Nervous system disorders</p> <p>Dizziness</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysgeusia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypoaesthesia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neuropathy peripheral</p> <p>alternative assessment type: Non-systematic</p> | <p>27 / 219 (12.33%)</p> <p>30</p> <p>44 / 219 (20.09%)</p> <p>58</p> <p>37 / 219 (16.89%)</p> <p>53</p> <p>19 / 219 (8.68%)</p> <p>21</p> | <p>22 / 223 (9.87%)</p> <p>28</p> <p>31 / 223 (13.90%)</p> <p>39</p> <p>68 / 223 (30.49%)</p> <p>95</p> <p>7 / 223 (3.14%)</p> <p>9</p> |  |

|  |   |  |  |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Paraesthesia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Peripheral sensory neuropathy</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>29 / 219 (13.24%)</p> <p>36</p> <p>23 / 219 (10.50%)</p> <p>28</p> <p>26 / 219 (11.87%)</p> <p>26</p>  | <p>21 / 223 (9.42%)</p> <p>37</p> <p>11 / 223 (4.93%)</p> <p>14</p> <p>26 / 223 (11.66%)</p> <p>27</p> |  |
| <p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>81 / 219 (36.99%)</p> <p>103</p> <p>59 / 219 (26.94%)</p> <p>92</p> <p>24 / 219 (10.96%)</p> <p>36</p> | <p>43 / 223 (19.28%)</p> <p>47</p> <p>13 / 223 (5.83%)</p> <p>20</p> <p>18 / 223 (8.07%)</p> <p>23</p> |  |
| <p>Eye disorders</p> <p>Dry eye</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lacrimation increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>14 / 219 (6.39%)</p> <p>16</p> <p>18 / 219 (8.22%)</p> <p>21</p>                                       | <p>16 / 223 (7.17%)</p> <p>16</p> <p>6 / 223 (2.69%)</p> <p>9</p>                                      |  |
| <p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>alternative assessment type: Non-systematic</p>   |   |  |  |

|   |                    |                    |
|---|--------------------|--------------------|
| subjects affected / exposed                 | 30 / 219 (13.70%)  | 21 / 223 (9.42%)   |
| occurrences (all)                           | 45                 | 29                 |
| Abdominal pain upper                        |                    |                    |
| alternative assessment type: Non-systematic |                    |                    |
| subjects affected / exposed                 | 22 / 219 (10.05%)  | 7 / 223 (3.14%)    |
| occurrences (all)                           | 29                 | 8                  |
| Constipation                                |                    |                    |
| alternative assessment type: Non-systematic |                    |                    |
| subjects affected / exposed                 | 43 / 219 (19.63%)  | 34 / 223 (15.25%)  |
| occurrences (all)                           | 48                 | 52                 |
| Diarrhoea                                   |                    |                    |
| alternative assessment type: Non-systematic |                    |                    |
| subjects affected / exposed                 | 163 / 219 (74.43%) | 86 / 223 (38.57%)  |
| occurrences (all)                           | 372                | 179                |
| Dry mouth                                   |                    |                    |
| alternative assessment type: Non-systematic |                    |                    |
| subjects affected / exposed                 | 4 / 219 (1.83%)    | 27 / 223 (12.11%)  |
| occurrences (all)                           | 4                  | 33                 |
| Dyspepsia                                   |                    |                    |
| alternative assessment type: Non-systematic |                    |                    |
| subjects affected / exposed                 | 15 / 219 (6.85%)   | 25 / 223 (11.21%)  |
| occurrences (all)                           | 18                 | 30                 |
| Gastrooesophageal reflux disease            |                    |                    |
| alternative assessment type: Non-systematic |                    |                    |
| subjects affected / exposed                 | 16 / 219 (7.31%)   | 7 / 223 (3.14%)    |
| occurrences (all)                           | 18                 | 8                  |
| Haemorrhoids                                |                    |                    |
| alternative assessment type: Non-systematic |                    |                    |
| subjects affected / exposed                 | 14 / 219 (6.39%)   | 5 / 223 (2.24%)    |
| occurrences (all)                           | 19                 | 5                  |
| Nausea                                      |                    |                    |
| alternative assessment type: Non-systematic |                    |                    |
| subjects affected / exposed                 | 139 / 219 (63.47%) | 103 / 223 (46.19%) |
| occurrences (all)                           | 249                | 248                |

|   |   |   |  |
|---|---|---|--|
| <p>Stomatitis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>49 / 219 (22.37%)</p> <p>70</p>  | <p>23 / 223 (10.31%)</p> <p>30</p>  |  |
| <p>Vomiting</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>68 / 219 (31.05%)</p> <p>83</p>  | <p>35 / 223 (15.70%)</p> <p>47</p>  |  |
| <p>Gingival bleeding</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 219 (0.46%)</p> <p>1</p>   | <p>15 / 223 (6.73%)</p> <p>17</p>   |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>Alopecia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dermatitis acneiform</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry skin</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nail discolouration</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nail disorder</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>alternative assessment type: Non-systematic</p> | <p>146 / 219 (66.67%)</p> <p>149</p> <p>16 / 219 (7.31%)</p> <p>16</p> <p>27 / 219 (12.33%)</p> <p>32</p> <p>20 / 219 (9.13%)</p> <p>21</p> <p>11 / 219 (5.02%)</p> <p>13</p> | <p>37 / 223 (16.59%)</p> <p>38</p> <p>12 / 223 (5.38%)</p> <p>14</p> <p>30 / 223 (13.45%)</p> <p>32</p> <p>0 / 223 (0.00%)</p> <p>0</p> <p>2 / 223 (0.90%)</p> <p>2</p> |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 26 / 219 (11.87%) | 20 / 223 (8.97%)  |  |
| occurrences (all)                               | 34                | 22                |  |
| Rash  |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 57 / 219 (26.03%) | 43 / 223 (19.28%) |  |
| occurrences (all)                               | 77                | 60                |  |
| Erythema  |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 8 / 219 (3.65%)   | 16 / 223 (7.17%)  |  |
| occurrences (all)                               | 10                | 18                |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Arthralgia                                      |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 41 / 219 (18.72%) | 31 / 223 (13.90%) |  |
| occurrences (all)                               | 55                | 37                |  |
| Back pain                                       |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 20 / 219 (9.13%)  | 14 / 223 (6.28%)  |  |
| occurrences (all)                               | 22                | 20                |  |
| Bone pain                                       |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 17 / 219 (7.76%)  | 8 / 223 (3.59%)   |  |
| occurrences (all)                               | 25                | 8                 |  |
| Muscle spasms                                   |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 14 / 219 (6.39%)  | 20 / 223 (8.97%)  |  |
| occurrences (all)                               | 16                | 21                |  |
| Musculoskeletal pain                            |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 20 / 219 (9.13%)  | 10 / 223 (4.48%)  |  |
| occurrences (all)                               | 22                | 10                |  |
| Myalgia   |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |

|  |  |  |  |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>37 / 219 (16.89%)</p> <p>41</p> <p>13 / 219 (5.94%)</p> <p>16</p>                                   | <p>28 / 223 (12.56%)</p> <p>42</p> <p>15 / 223 (6.73%)</p> <p>15</p>                                   |  |
| <p>Infections and infestations</p> <p>Nasopharyngitis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper respiratory tract infection</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urinary tract infection</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>23 / 219 (10.50%)</p> <p>29</p> <p>15 / 219 (6.85%)</p> <p>18</p> <p>17 / 219 (7.76%)</p> <p>20</p> | <p>29 / 223 (13.00%)</p> <p>34</p> <p>21 / 223 (9.42%)</p> <p>24</p> <p>12 / 223 (5.38%)</p> <p>16</p> |  |
| <p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypokalaemia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypomagnesaemia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                    | <p>40 / 219 (18.26%)</p> <p>46</p> <p>20 / 219 (9.13%)</p> <p>23</p> <p>13 / 219 (5.94%)</p> <p>13</p> | <p>33 / 223 (14.80%)</p> <p>41</p> <p>13 / 223 (5.83%)</p> <p>17</p> <p>0 / 223 (0.00%)</p> <p>0</p>   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 21 September 2014 | Wording regarding the timing between neoadjuvant treatment and surgery was aligned in the protocol synopsis. The Investigational Medicinal Product was updated to provide guidance to refer to national prescribing information for contraindications, adverse reactions, warnings, and precautions for docetaxel and carboplatin. The inclusion and exclusion criteria was updated. The study schema was updated. Language in the Permitted Therapy section was updated. Language was updated in the section with patients receiving optional adjuvant chemotherapy. Language regarding post-study adverse events reporting was updated. Language regarding pulmonary toxicity was clarified. Information regarding potential neurotoxicity was updated and a section on extravasation was added. Clarifications were updated regarding dose modifications/delays in response to trastuzumab emtansine-specific adverse events. Appendix 11 was added to provide guidance on carboplatin dosing for patients for whom the isotope dilution mass spectrometry method of serum creatine measurement is used. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported