



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 | |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 19 December 2016 |
| First version publication date | 19 December 2016 |

Trial information

Trial identification

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

Additional study identifiers

| | |
|------------------------------------|---------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02131064 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Other identifier: TRIO021 |

Notes:

Sponsors

| | |
|------------------------------|--------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, Roche Trial Information Hotline, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, Roche Trial Information Hotline, +41 61 6878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|------------------------------------------------------|------------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 03 December 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 December 2015 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial were to compare the total pathological Complete Response (tpCR) rate (ypT0/is, ypN0) and safety among chemotherapy, Trastuzumab (TCH) + Pertuzumab (P) (Arm A) and Trastuzumab Emtansine (T-DM1) + P (Arm B).

Protection of trial subjects:

This study was conducted in full conformance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), and was conducted under a U.S. Investigational New Drug application, complying with Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws.

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 | Ukraine: 5 |
| Country: Number of subjects enrolled | Belgium: 30 |
| Country: Number of subjects enrolled | Spain: 88 |
| Country: Number of subjects enrolled | France: 27 |
| Country: Number of subjects enrolled | Taiwan: 42 |
| Country: Number of subjects enrolled | Germany: 24 |
| 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 68 sites in 10 countries, of which 444 participants were randomized in two arms: TCH + P (Arm A) and T-DM1 + P (Arm B).

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall Period (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/m²) 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 | Active comparator |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | Herceptin® |
| Pharmaceutical forms | Powder 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 | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate 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 | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel 75 mg/m² IV infusion q3w

| | |
|----------------------------------------|---------------------------------------|
| Investigational medicinal product name | Pertuzumab |
| Investigational medicinal product code | RO4368451 |
| Other name | Perjeta® |
| Pharmaceutical forms | 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

| | |
|------------------|-----------|
| Arm title | 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 | RO5304020 |
| Other name | Kadcyla® |
| Pharmaceutical forms | Powder 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 | RO4368451 |
| Other name | Perjeta® |
| Pharmaceutical forms | 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

| Number of subjects in period 1 | TCH + P | T-DM1 + P |
|---------------------------------------|---------|-----------|
| Started | 221 | 223 |
| Completed | 0 | 0 |
| Not completed | 221 | 223 |
| Consent withdrawn by subject | 6 | 14 |
| Death | - | 1 |
| Ongoing | 214 | 207 |
| Unspecified | 1 | - |
| Lost to follow-up | - | 1 |

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/m²) 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 Units: Subjects | | | |

| | | | |
|-------------------------------------------------------------------------|----------------|----------------|-----|
| Age continuous Units: years arithmetic mean standard deviation | 49.3 ± 11.2 | 50.5 ± 10.6 | - |
| Gender categorical Units: Subjects | | | |
| Female | 221 | 222 | 443 |
| Male | 0 | 1 | 1 |

End points

End points 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 ²) 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). | |

Primary: Percentage of Participants With tpCR Assessed Based on Tumor Samples

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| End point title | Percentage of Participants With tpCR Assessed Based on Tumor Samples |
| End point description: | |
| 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 participants with tpCR was reported. Intent-to-treat (ITT) population comprised all randomized participants, whether or not they received any study treatment or completed a full course of study treatment. Participants were analyzed according to their randomized treatment. | |
| End point type | Primary |
| End point timeframe: | |
| 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 participants | | | | |
| number (confidence interval 95%) | 55.7 (48.84 to 62.32) | 44.4 (37.76 to 51.18) | | |

Statistical analyses

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| 95% CI for the difference in tPCR rates between treatment arms was calculated using normal approximation. The Cochran-Mantel-Haenszel Chi-square test was used and stratified by local hormone receptor status and clinical stage at presentation. | |

| | |
|-----------------------------------------|------------------------------------|
| Comparison groups | TCH + P v T-DM1 + P |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0155 ^[1] |
| Method | Cochran-Mantel-Haenszel Chi-Square |
| Parameter estimate | Difference in tpCR rate |
| Point estimate | -11.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.5 |
| upper limit | -2.02 |

Notes:

[1] - Threshold for significance at 5%

Secondary: Event-free Survival (EFS) Assessed by Investigator Based on Radiological, Clinical and Histological Assessment

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Event-free Survival (EFS) Assessed by Investigator Based on Radiological, Clinical and Histological Assessment |
| 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. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization up to disease progression or recurrence or death (up to approximately 45 months) | |

| End point values | TCH + P | T-DM1 + P | | |
|-------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: months | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[2] - The data for this endpoint will be reported after final analysis.

[3] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Invasive Disease-free Survival (IDFS)

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| End point title | Invasive Disease-free Survival (IDFS) |
| End point description: | |
| IDFS is defined only for participants who undergo surgery. Participants who do not undergo surgery will be excluded from the analysis. IDFS is defined as the time from surgery to the first documented occurrence of an IDFS event, defined as: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast as the original primary lesion); Ipsilateral local–regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); Distant recurrence (i.e., evidence of breast cancer, excluding ipsilateral invasive or local-regional breast cancer, in any anatomic site that has been either histologically confirmed or clinically diagnosed as recurrent invasive breast cancer); Contralateral | |

invasive breast cancer; and death from any cause.

| | |
|-----------------------------------------------------------------------------------------------|-----------|
| 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 | 0 ^[4] | 0 ^[5] | | |
| Units: months | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[4] - The data for this endpoint will be reported after final analysis.

[5] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-------------------------------------------------------------------------------------|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall survival is defined as the time from randomization to death from any cause. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until death (up to approximately 45 months) | |

| End point values | TCH + P | T-DM1 + P | | |
|-------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | | |
| Units: months | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[6] - The data for this endpoint will be reported after final analysis.

[7] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

BCS rate was defined as the percentage of participants who achieve BCS out of the ITT population of participants without inflammatory breast cancer. A subset of ITT population including participants who had non-inflammatory breast cancer at baseline. Participants were analyzed according to their

randomized treatment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

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

Statistical analyses

| | |
|---------------------------------------------------------------------------------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| 95% CI for the difference in BCS rate between treatment arms was calculated using normal approximation. | |
| Comparison groups | TCH + P v T-DM1 + P |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| 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 Participants With Selected Adverse Events (AEs)

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| End point title | Percentage of Participants With Selected Adverse Events (AEs) |
| End point description: | |
| Selected AEs included hepatotoxicity, pulmonary toxicity, cardiac dysfunction, neutropenia, thrombocytopenia, peripheral neuropathy, hemorrhage, infusion related reaction (IRR)/hypersensitivity, IRR/hypersensitivity symptoms, rash, diarrhoea and mucositis. Safety population comprised all participants who received at least one full or partial dose of any study treatment. Participants were analyzed according to the treatment they actually received. 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: | |
| Neoadjuvant phase (Baseline up to Cycle 6, each cycle = 21 days) | |

| End point values | TCH + P | T-DM1 + P | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 219 | 223 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Hepatotoxicity | 11.9 | 24.2 | | |
| Pulmonary Toxicity | 0 | 0.9 | | |
| Cardiac Dysfunction | 0.9 | 0.4 | | |
| Neutropenia | 45.2 | 0.9 | | |
| Thrombocytopenia | 21.9 | 7.6 | | |
| Peripheral Neuropathy | 30.1 | 9.9 | | |
| Hemorrhage | 14.6 | 20.2 | | |
| IRR/Hypersensitivity | 11.9 | 17.9 | | |
| IRR/Hypersensitivity symptoms | 5.9 | 13.9 | | |
| Rash | 34.7 | 21.5 | | |
| Diarrhoea | 73.5 | 33.2 | | |
| Mucositis | 40.2 | 15.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Response for Neuropathy Single Item

| | |
|-----------------|-------------------------------------------------------------------|
| End point title | Percentage of Participants by Response for Neuropathy Single Item |
|-----------------|-------------------------------------------------------------------|

End point description:

Participants answered the question "Did you have tingling hands/feet?", from the Modified Quality of Life Questionnaire Breast Cancer 23 (mQLQ-BR23), on a 4-point scale (1 'Not at all', 2 'a little', 3 'quite a bit' 4 'Very much'). Percentage of participants by each response was reported. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified categories. Percentage values are based on ITT N.

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

End point timeframe:

Baseline, Cycle 3, Cycle 5 of neoadjuvant period (each cycle = 21 days); pre-surgery visit (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 | 194 | 205 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Not at all: Baseline (n= 194, 205) | 76.9 | 80.7 | | |
| A little bit: Baseline (n= 194, 205) | 9.5 | 10.3 | | |

| | | | | |
|-----------------------------------------|------|------|--|--|
| Somewhat: Baseline (n= 194, 205) | 0 | 0 | | |
| Quite a bit: Baseline (n= 194, 205) | 0.9 | 0.9 | | |
| Very much: Baseline (n= 194, 205) | 0.5 | 0 | | |
| Not at all: Cycle 3 (n= 181, 190) | 55.2 | 61.9 | | |
| A little bit: Cycle 3 (n= 181, 190) | 20.8 | 20.2 | | |
| Somewhat: Cycle 3 (n= 181, 190) | 0 | 0 | | |
| Quite a bit: Cycle 3 (n= 181, 190) | 3.6 | 2.7 | | |
| Very much: Cycle 3 (n= 181, 190) | 2.3 | 0.4 | | |
| Not at all: Cycle 5 (n= 181, 182) | 37.1 | 55.2 | | |
| A little bit: Cycle 5 (n= 181, 182) | 29.9 | 22 | | |
| Somewhat: Cycle 5 (n= 181, 182) | 0 | 0 | | |
| Quite a bit: Cycle 5 (n= 181, 182) | 8.1 | 2.7 | | |
| Very much: Cycle 5 (n= 181, 182) | 6.8 | 1.8 | | |
| Not at all: Pre-Surgery (n= 172, 176) | 24 | 53.4 | | |
| A little bit: Pre-Surgery (n= 172, 176) | 28.1 | 18.8 | | |
| Somewhat: Pre-Surgery (n= 172, 176) | 0 | 0 | | |
| Quite a bit: Pre-Surgery (n= 172, 176) | 15.8 | 5.4 | | |
| Very much: Pre-Surgery (n= 172, 176) | 10 | 1.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Response for Skin Problem Single Items

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

End point description:

Participants answered the Question 1 "Did itching skin bother you?" and Question 2 "Have you had skin problems?", from the mQLQ-BR23, on a 4-point scale (1 'Not at all', 2 'a little', 3 'quite a bit' 4 'Very much'). Percentage of participants by each response was reported. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified categories. Percentage values are based on ITT N.

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

End point timeframe:

Baseline, Cycle 3, Cycle 5 of neoadjuvant period (each cycle = 21 days); pre-surgery visit (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 | 194 | 205 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Question 1: Not at all: Baseline (n= 193, 205) | 70.6 | 72.6 | | |
| Question 1: A little bit: Baseline (n= 193, 205) | 14.5 | 16.6 | | |
| Question 1: Somewhat: Baseline (n= 193, 205) | 0 | 0 | | |

| | | | | |
|-----------------------------------------------------|------|------|--|--|
| Question 1: Quite a bit: Baseline (n= 193, 205) | 2.3 | 2.2 | | |
| Question 1: Very much: Baseline (n= 193, 205) | 0 | 0.4 | | |
| Question 1: Not at all: Cycle 3 (n= 180, 190) | 35.3 | 50.7 | | |
| Question 1: A little bit: Cycle 3 (n= 180, 190) | 32.1 | 28.3 | | |
| Question 1: Somewhat: Cycle 3 (n= 180, 190) | 0 | 0 | | |
| Question 1: Quite a bit: Cycle 3 (n= 180, 190) | 11.8 | 4.5 | | |
| Question 1: Very much: Cycle 3 (n= 180, 190) | 2.3 | 1.8 | | |
| Question 1: Not at all: Cycle 5 (n= 180, 182) | 48.9 | 48 | | |
| Question 1: A little bit: Cycle 5 (n= 180, 182) | 22.6 | 25.6 | | |
| Question 1: Somewhat: Cycle 5 (n= 180, 182) | 0 | 0 | | |
| Question 1: Quite a bit: Cycle 5 (n= 180, 182) | 7.7 | 6.7 | | |
| Question 1: Very much: Cycle 5 (n= 180, 182) | 2.3 | 1.3 | | |
| Question 1: Not at all: Pre-Surgery (n= 172, 176) | 40.7 | 49.3 | | |
| Question 1: A little bit: Pre-Surgery (n= 172, 176) | 27.1 | 22.4 | | |
| Question 1: Somewhat: Pre-Surgery (n= 172, 176) | 0 | 0 | | |
| Question 1: Quite a bit: Pre-Surgery (n= 172, 176) | 7.7 | 5.8 | | |
| Question 1: Very much: Pre-Surgery (n= 172, 176) | 2.3 | 1.3 | | |
| Question 2: Not at all: Baseline (n= 194, 205) | 64.3 | 66.8 | | |
| Question 2: A little bit: Baseline (n= 194, 205) | 19.9 | 18.4 | | |
| Question 2: Somewhat: Baseline (n= 194, 205) | 0 | 0 | | |
| Question 2: Quite a bit: Baseline (n= 194, 205) | 3.2 | 6.3 | | |
| Question 2: Very much: Baseline (n= 194, 205) | 0.5 | 0.4 | | |
| Question 2: Not at all: Cycle 3 (n= 181, 190) | 13.6 | 25.1 | | |
| Question 2: A little bit: Cycle 3 (n= 181, 190) | 40.7 | 40.4 | | |
| Question 2: Somewhat: Cycle 3 (n= 181, 190) | 0 | 0 | | |
| Question 2: Quite a bit: Cycle 3 (n= 181, 190) | 20.4 | 15.2 | | |
| Question 2: Very much: Cycle 3 (n= 181, 190) | 7.2 | 4.5 | | |
| Question 2: Not at all: Cycle 5 (n= 181, 182) | 21.3 | 26.9 | | |
| Question 2: A little bit: Cycle 5 (n= 181, 182) | 35.7 | 37.2 | | |
| Question 2: Somewhat: Cycle 5 (n= 181, 182) | 0 | 0 | | |
| Question 2: Quite a bit: Cycle 5 (n= 181, 182) | 19.9 | 13.5 | | |

| | | | | |
|----------------------------------------------------|------|------|--|--|
| Question 2: Very much: Cycle 5 (n= 181, 182) | 5 | 4 | | |
| Question 2: Not at all: Pre-Surgery (n= 172, 176) | 20.8 | 28.7 | | |
| Question 2:A little bit: Pre-Surgery (n= 172, 176) | 33.9 | 37.2 | | |
| Question 2: Somewhat: Pre-Surgery (n= 172, 176) | 0 | 0 | | |
| Question 2: Quite a bit: Pre-Surgery (n= 172, 176) | 16.7 | 9 | | |
| Question 2: Very much: Pre-Surgery (n= 172, 176) | 6.3 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Response for Hair Loss Single Item

| | |
|-----------------|------------------------------------------------------------------|
| End point title | Percentage of Participants by Response for Hair Loss Single Item |
|-----------------|------------------------------------------------------------------|

End point description:

Participants answered the Question "Have you lost any hair?", from the mQLQ-BR23, on a 4-point scale (1 'Not at all', 2 'a little', 3 'quite a bit' 4 'Very much'). Percentage of participants by each response was reported. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified categories. Percentage values are based on ITT N.

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

End point timeframe:

Baseline, Cycle 3, Cycle 5 of neoadjuvant period (each cycle = 21 days); pre-surgery visit (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 | 194 | 205 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Not at all: Baseline (n= 194, 205) | 79.6 | 87.4 | | |
| A little bit: Baseline (n= 194, 205) | 7.7 | 4.5 | | |
| Somewhat: Baseline (n= 194, 205) | 0 | 0 | | |
| Quite a bit: Baseline (n= 194, 205) | 0.5 | 0 | | |
| Very much: Baseline (n= 194, 205) | 0 | 0 | | |
| Not at all: Cycle 3 (n= 181, 190) | 8.6 | 67.3 | | |
| A little bit: Cycle 3 (n= 181, 190) | 11.8 | 17.5 | | |
| Somewhat: Cycle 3 (n= 181, 190) | 0 | 0 | | |
| Quite a bit: Cycle 3 (n= 181, 190) | 20.8 | 0.4 | | |
| Very much: Cycle 3 (n= 181, 190) | 40.7 | 0 | | |
| Not at all: Cycle 5 (n= 181, 182) | 20.4 | 59.2 | | |
| A little bit: Cycle 5 (n= 181, 182) | 19.9 | 20.2 | | |
| Somewhat: Cycle 5 (n= 181, 182) | 0 | 0 | | |
| Quite a bit: Cycle 5 (n= 181, 182) | 15.4 | 1.8 | | |

| | | | | |
|-----------------------------------------|------|------|--|--|
| Very much: Cycle 5 (n= 181, 182) | 26.2 | 0.4 | | |
| Not at all: Pre-Surgery (n= 172, 176) | 31.7 | 51.6 | | |
| A little bit: Pre-Surgery (n= 172, 176) | 12.7 | 25.1 | | |
| Somewhat: Pre-Surgery (n= 172, 176) | 0 | 0 | | |
| Quite a bit: Pre-Surgery (n= 172, 176) | 11.3 | 2.2 | | |
| Very much: Pre-Surgery (n= 172, 176) | 22.2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Clinically Meaningful Deterioration in Global Health Status (GHS)/Quality of Life (QoL) Score

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

End point description:

Participants 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. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure.

| | |
|----------------|-----------|
| 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 participants | | | | |
| number (not applicable) | 69.9 | 45.4 | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

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 | superiority |
| 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: | |
| <p>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. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure.</p> | |
| 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 | Statistical Analysis 1 |
| Statistical analysis description: | |
| <p>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).</p> | |
| Comparison groups | TCH + P v T-DM1 + P |

| | |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 391 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| 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 Participants With a Clinically Meaningful Deterioration in Function Subscales

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Clinically Meaningful Deterioration in Function Subscales |
| 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. Clinically meaningful deterioration was defined as a decrease in score of 10 points in physical function and HRQoL; decrease of 7 points in cognitive function and decrease of 14 points in role function. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure. | |
| 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 participants | | | | |
| number (not applicable) | | | | |
| Cognitive Functioning | 59.1 | 42.4 | | |
| Physical Functioning | 72.5 | 40 | | |
| Role Functioning | 76.7 | 47.8 | | |

Statistical analyses

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| 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 | superiority |
| Parameter estimate | Difference in Deterioration |
| Point estimate | -16.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.32 |
| upper limit | -6.94 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

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 | superiority |
| Parameter estimate | Difference in Deterioration |
| Point estimate | -32.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -41.74 |
| upper limit | -23.34 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

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 | superiority |
| Parameter estimate | Difference in Deterioration |
| Point estimate | -28.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -37.95 |
| upper limit | -19.8 |

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. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure. Here, 99999 represents data not estimable. | |
| 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%) | | | | |
| Physical Function | 2.79 (2.79 to 2.96) | 4.86 (4.4 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 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Clinically Meaningful Increase in Symptom Subscales

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Clinically Meaningful Increase in Symptom Subscales |
| End point description: | |
| Participants 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, dyspnoea; increase of 9 points in insomnia; increase of 14 points in appetite loss; increase of 15 points in diarrhoea, constipation; increase of 10 points in fatigue, systemic therapy side effects, hair loss. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified categories. | |
| 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 participants | | | | |
| number (not applicable) | | | | |
| Appetite Loss (n=193, 205) | 61.1 | 47.8 | | |
| Any Hair Loss (n=194, 205) | 91.2 | 40.5 | | |
| Systemic Therapy Side-Effects (n=194, 205) | 89.7 | 75.1 | | |
| Constipation (n=193, 205) | 33.2 | 32.7 | | |
| Diarrhoea (n=193, 205) | 79.3 | 50.7 | | |
| Dyspnea (n=193, 205) | 56 | 31.2 | | |
| Fatigue (n=193, 205) | 87.6 | 68.8 | | |
| Nausea/Vomiting (n=193, 205) | 66.3 | 43.9 | | |
| Pain (n=193, 205) | 56 | 36.6 | | |
| Insomnia (n=193, 205) | 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 ^[8] |
|-----------------|---------------------------------------------------------------------------|

End point description:

Only participants who received trastuzumab were to be analyzed for this outcome. Pharmacokinetic (PK) population comprised all participants who received at least one treatment dose of trastuzumab emtansine (in T-DM1 + P arm) or trastuzumab (in TCH + P arm), and had at least one post-treatment serum or plasma sample. Number of participants analyzed = Number of participants in PK Population evaluable for this outcome. Here 'n' signifies number of participants evaluable for specified category.

| | |
|----------------|-----------|
| 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 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: Trastuzumab was administered in this arm only.

| End point values | TCH + P | | | |
|-------------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 162 | | | |
| Units: micrograms per milliliter (mcg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n=162) | 167 (± 47.1) | | | |
| Cycle 6 (n=155) | 148 (± 44.7) | | | |

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 ^[9] |
|-----------------|--------------------------------------------------------------------|

End point description:

Only participants who received trastuzumab emtansine were to be analyzed for this outcome. PK population. Number of participants analyzed = Number of participants in the PK Population evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified category.

| | |
|----------------|-----------|
| 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 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: Trastuzumab emtansine was administered in this arm only.

| End point values | T-DM1 + P | | | |
|----------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 207 | | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Trastuzumab emtansine: Cycle 1 (n=206) | 80.3 (± 26.6) | | | |
| Trastuzumab emtansine: Cycle 6 (n=179) | 72.3 (± 30) | | | |
| Total Trastuzumab: Cycle 1 (n=207) | 79 (± 25.7) | | | |
| Total Trastuzumab: Cycle 6 (n=179) | 79.5 (± 30.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Trastuzumab Emtansine and Total Trastuzumab

| | |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Minimum Observed Serum Concentration (Cmin) of Trastuzumab Emtansine and Total Trastuzumab ^[10] |
|-----------------|------------------------------------------------------------------------------------------------------------|

End point description:

Only participants who received trastuzumab emtansine were to be analyzed for this outcome. PK population. Number of participants analyzed = Number of participants in the PK population evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified category.

| | |
|----------------|-----------|
| 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 period

Notes:

[10] - 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: Trastuzumab emtansine was administered in this arm only.

| End point values | T-DM1 + P | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 191 | | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Trastuzumab emtansine: (n=190) | 3.06 (± 7.68) | | | |
| Total Trastuzumab: (n=191) | 12.5 (± 8.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of Trastuzumab

| | |
|-----------------|-------------------------------------|
| End point title | Cmin of Trastuzumab ^[11] |
|-----------------|-------------------------------------|

End point description:

Only participants who received trastuzumab were to be analyzed for this outcome. PK population. Number of participants analyzed = Number of participants in PK Population with evaluable samples at a given timepoint.

| | |
|----------------|-----------|
| 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 period

Notes:

[11] - 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: Trastuzumab was administered in this arm only.

| End point values | TCH + P | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 165 | | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | 45.8 (± 17.8) | | | |

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 ^[12] |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

DM1 is the metabolite of trastuzumab emtansine. Only participants who received trastuzumab emtansine were to be analyzed for this outcome. PK population. Number of participants analyzed = Number of participants in the PK population evaluable for this outcome measure.

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

End point timeframe:

Pre-study treatment infusion (0 hr) (infusion duration = 90 min) on Day 1 of Cycle 1 (cycle length = 21

days); 15-30 min post-study treatment infusion on Day 1 of Cycle 1 and 6 in neoadjuvant period

Notes:

[12] - 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: Trastuzumab emtansine was administered in this arm only.

| End point values | T-DM1 + P | | | |
|-----------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 221 | | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1: Pre-dose (n=211) | 0.0841 (\pm 0.881) | | | |
| Cycle 1: 15-30 min post-dose (n=209) | 4.98 (\pm 2.82) | | | |
| Cycle 6: 15-30 min post-dose (n=180) | 4.85 (\pm 2.74) | | | |

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) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Pre-study treatment infusion (0 hr) (infusion duration = 90 min) on Day 1 of Cycle 1 (cycle length = 21 days) in neoadjuvant period; 15-30 min post-study treatment infusion on Day 1 of Cycle 1 and 6 in neoadjuvant and adjuvant period

| End point values | TCH + P | T-DM1 + P | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[13] | 0 ^[14] | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[13] - The data for this endpoint will be reported after final analysis.

[14] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Therapeutic Antibodies (ATA) to

TDM-1

| | |
|-----------------|--------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Anti-Therapeutic Antibodies (ATA) to TDM-1 ^[15] |
|-----------------|--------------------------------------------------------------------------------------------|

End point description:

Participants were considered post-baseline ATA positive if they had ATAs post-baseline that were either treatment-induced or treatment-enhanced. Participants had treatment-induced ATAs if they had a negative or missing ATA result at baseline, and at least one positive ATA result post-baseline. Participants 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. ITT population, including participants from T-DM1 + P arm only. Number of participants analyzed = participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified category.

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

End point timeframe:

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

Notes:

[15] - 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: Trastuzumab emtansine was administered in this arm only.

| End point values | T-DM1 + P | | | |
|---------------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 216 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Neoadjuvant Phase: At Baseline (n=216) | 5.6 | | | |
| Neoadjuvant Phase: At Post-Baseline (n=201) | 8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ATA to Trastuzumab

| | |
|-----------------|----------------------------------------------------|
| End point title | Percentage of Participants With ATA to Trastuzumab |
|-----------------|----------------------------------------------------|

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

| End point values | TCH + P | T-DM1 + P | | |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[16] - The data for this endpoint will be reported after final analysis.

[17] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

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 | Non-systematic |
|-----------------|----------------|

Dictionary used

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

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| Dictionary version | 18.1 |
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Reporting groups

| | |
|-----------------------|-----------|
| 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 title | TCH + P |
|-----------------------|---------|

Reporting group description:

Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion, trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 mg/m² IV infusion and carboplatin at a dose to achieve an AUC of 6 mg/mL*min IV infusion 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).

| Serious adverse events | T-DM1 + P | TCH + P | |
|---------------------------------------------------------------------|------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 223 (4.93%) | 63 / 219 (28.77%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |

| | | | |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 2 / 219 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast haematoma | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 223 (0.90%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (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 | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 3 / 219 (1.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Procedural intestinal perforation | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous haematoma | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| 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 | 1 / 223 (0.45%) | 2 / 219 (0.91%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|-------------------------------------------------|-----------------|-------------------|--|
| subjects affected / exposed | 1 / 223 (0.45%) | 1 / 219 (0.46%) | |
| 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 | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 223 (1.35%) | 26 / 219 (11.87%) | |
| occurrences causally related to treatment / all | 0 / 3 | 33 / 33 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 223 (1.35%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 7 / 219 (3.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 1 / 219 (0.46%) | |
| 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 | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 3 / 219 (1.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 9 / 219 (4.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (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 | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 4 / 219 (1.83%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cellulitis | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 223 (0.00%) | 2 / 219 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 223 (0.90%) | 2 / 219 (0.91%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 2 / 219 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| 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 | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 2 / 223 (0.90%) | 0 / 219 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 219 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 2 / 219 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | T-DM1 + P | TCH + P | |
|-------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 198 / 223 (88.79%) | 215 / 219 (98.17%) | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 17 / 223 (7.62%) | 30 / 219 (13.70%) | |
| occurrences (all) | 20 | 32 | |
| Hypertension | | | |
| subjects affected / exposed | 10 / 223 (4.48%) | 14 / 219 (6.39%) | |
| occurrences (all) | 10 | 16 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 39 / 223 (17.49%) | 57 / 219 (26.03%) | |
| occurrences (all) | 59 | 102 | |
| Chills | | | |

| | | | |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 23 / 223 (10.31%) | 9 / 219 (4.11%) | |
| occurrences (all) | 26 | 9 | |
| Fatigue | | | |
| subjects affected / exposed | 74 / 223 (33.18%) | 93 / 219 (42.47%) | |
| occurrences (all) | 106 | 133 | |
| Influenza like illness | | | |
| subjects affected / exposed | 13 / 223 (5.83%) | 6 / 219 (2.74%) | |
| occurrences (all) | 15 | 7 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 18 / 223 (8.07%) | 30 / 219 (13.70%) | |
| occurrences (all) | 21 | 36 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 223 (2.24%) | 27 / 219 (12.33%) | |
| occurrences (all) | 5 | 34 | |
| Pyrexia | | | |
| subjects affected / exposed | 30 / 223 (13.45%) | 29 / 219 (13.24%) | |
| occurrences (all) | 41 | 39 | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 15 / 223 (6.73%) | 9 / 219 (4.11%) | |
| occurrences (all) | 16 | 9 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 26 / 223 (11.66%) | 15 / 219 (6.85%) | |
| occurrences (all) | 31 | 18 | |
| Epistaxis | | | |
| subjects affected / exposed | 35 / 223 (15.70%) | 24 / 219 (10.96%) | |
| occurrences (all) | 62 | 29 | |
| Dyspnoea | | | |
| subjects affected / exposed | 13 / 223 (5.83%) | 14 / 219 (6.39%) | |
| occurrences (all) | 15 | 18 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 7 / 223 (3.14%) | 11 / 219 (5.02%) | |
| occurrences (all) | 8 | 14 | |
| Psychiatric disorders | | | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| Depression subjects affected / exposed occurrences (all) | 8 / 223 (3.59%) 8 | 14 / 219 (6.39%) 14 | |
| Insomnia subjects affected / exposed occurrences (all) | 32 / 223 (14.35%) 36 | 29 / 219 (13.24%) 31 | |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 39 / 223 (17.49%) 50 | 18 / 219 (8.22%) 31 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 52 / 223 (23.32%) 65 | 23 / 219 (10.50%) 33 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 4 / 223 (1.79%) 5 | 22 / 219 (10.05%) 40 | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 13 / 223 (5.83%) 25 | 27 / 219 (12.33%) 38 | |
| Weight decreased subjects affected / exposed occurrences (all) | 13 / 223 (5.83%) 13 | 22 / 219 (10.05%) 22 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 4 / 223 (1.79%) 4 | 15 / 219 (6.85%) 16 | |
| Injury, poisoning and procedural complications Radiation skin injury subjects affected / exposed occurrences (all) | 9 / 223 (4.04%) 9 | 20 / 219 (9.13%) 20 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 18 / 223 (8.07%) 24 | 25 / 219 (11.42%) 27 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 30 / 223 (13.45%) 38 | 43 / 219 (19.63%) 54 | |

| | | | |
|--------------------------------------|-------------------|-------------------|--|
| Headache | | | |
| subjects affected / exposed | 62 / 223 (27.80%) | 35 / 219 (15.98%) | |
| occurrences (all) | 96 | 43 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 5 / 223 (2.24%) | 14 / 219 (6.39%) | |
| occurrences (all) | 6 | 15 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 15 / 223 (6.73%) | 27 / 219 (12.33%) | |
| occurrences (all) | 19 | 31 | |
| Paraesthesia | | | |
| subjects affected / exposed | 4 / 223 (1.79%) | 19 / 219 (8.68%) | |
| occurrences (all) | 5 | 23 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 16 / 223 (7.17%) | 22 / 219 (10.05%) | |
| occurrences (all) | 17 | 23 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 9 / 223 (4.04%) | 58 / 219 (26.48%) | |
| occurrences (all) | 11 | 85 | |
| Anaemia | | | |
| subjects affected / exposed | 30 / 223 (13.45%) | 78 / 219 (35.62%) | |
| occurrences (all) | 33 | 97 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 16 / 223 (7.17%) | 21 / 219 (9.59%) | |
| occurrences (all) | 18 | 27 | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 14 / 223 (6.28%) | 11 / 219 (5.02%) | |
| occurrences (all) | 14 | 13 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 4 / 223 (1.79%) | 17 / 219 (7.76%) | |
| occurrences (all) | 6 | 19 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 18 / 223 (8.07%) | 29 / 219 (13.24%) | |
| occurrences (all) | 24 | 38 | |
| Abdominal pain upper | | | |

| | | | |
|----------------------------------------|-------------------|--------------------|--|
| subjects affected / exposed | 4 / 223 (1.79%) | 18 / 219 (8.22%) | |
| occurrences (all) | 5 | 25 | |
| Diarrhoea | | | |
| subjects affected / exposed | 83 / 223 (37.22%) | 159 / 219 (72.60%) | |
| occurrences (all) | 157 | 354 | |
| Constipation | | | |
| subjects affected / exposed | 25 / 223 (11.21%) | 39 / 219 (17.81%) | |
| occurrences (all) | 38 | 42 | |
| Dry mouth | | | |
| subjects affected / exposed | 23 / 223 (10.31%) | 2 / 219 (0.91%) | |
| occurrences (all) | 29 | 2 | |
| Dyspepsia | | | |
| subjects affected / exposed | 22 / 223 (9.87%) | 15 / 219 (6.85%) | |
| occurrences (all) | 25 | 18 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 7 / 223 (3.14%) | 15 / 219 (6.85%) | |
| occurrences (all) | 8 | 17 | |
| Nausea | | | |
| subjects affected / exposed | 95 / 223 (42.60%) | 132 / 219 (60.27%) | |
| occurrences (all) | 200 | 235 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 4 / 223 (1.79%) | 14 / 219 (6.39%) | |
| occurrences (all) | 4 | 16 | |
| Vomiting | | | |
| subjects affected / exposed | 29 / 223 (13.00%) | 68 / 219 (31.05%) | |
| occurrences (all) | 35 | 86 | |
| Stomatitis | | | |
| subjects affected / exposed | 21 / 223 (9.42%) | 47 / 219 (21.46%) | |
| occurrences (all) | 28 | 65 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 31 / 223 (13.90%) | 142 / 219 (64.84%) | |
| occurrences (all) | 31 | 145 | |
| Dry skin | | | |
| subjects affected / exposed | 27 / 223 (12.11%) | 23 / 219 (10.50%) | |
| occurrences (all) | 28 | 28 | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 7 / 223 (3.14%) 8 | 13 / 219 (5.94%) 13 | |
| Nail disorder subjects affected / exposed occurrences (all) | 6 / 223 (2.69%) 6 | 14 / 219 (6.39%) 15 | |
| Nail discolouration subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 14 / 219 (6.39%) 15 | |
| Pruritus subjects affected / exposed occurrences (all) | 13 / 223 (5.83%) 15 | 16 / 219 (7.31%) 22 | |
| Rash subjects affected / exposed occurrences (all) | 42 / 223 (18.83%) 55 | 54 / 219 (24.66%) 70 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 19 / 223 (8.52%) 24 | 30 / 219 (13.70%) 41 | |
| Bone pain subjects affected / exposed occurrences (all) | 4 / 223 (1.79%) 4 | 14 / 219 (6.39%) 22 | |
| Back pain subjects affected / exposed occurrences (all) | 8 / 223 (3.59%) 12 | 17 / 219 (7.76%) 18 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 12 / 223 (5.38%) 13 | 7 / 219 (3.20%) 9 | |
| Myalgia subjects affected / exposed occurrences (all) | 26 / 223 (11.66%) 35 | 29 / 219 (13.24%) 31 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 7 / 223 (3.14%) 7 | 12 / 219 (5.48%) 14 | |
| Infections and infestations | | | |

| | | | |
|---------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 22 / 223 (9.87%) 24 | 15 / 219 (6.85%) 18 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 9 / 223 (4.04%) 12 | 14 / 219 (6.39%) 16 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 16 / 223 (7.17%) 17 | 9 / 219 (4.11%) 9 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 10 / 223 (4.48%) 14 | 20 / 219 (9.13%) 22 | |
| Decreased appetite subjects affected / exposed occurrences (all) | 26 / 223 (11.66%) 31 | 39 / 219 (17.81%) 46 | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 11 / 219 (5.02%) 11 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 September 2014 | <ul style="list-style-type: none">- Surgery was to be performed no later than 6 weeks after the last dose of neoadjuvant treatment instead of no later than 9 weeks.- The inclusion criterion was updated to clarify that participants with multifocal tumors must have had all discrete tumors sampled and centrally confirmed as Human Epidermal Growth Factor Receptor 2 (HER2)-positive.- Exclusion criteria were updated to clarify the eligibility of participants with prior breast in situ cancers (lobular carcinoma in situ, ductal carcinoma in situ) and participants who have received prior local and/or systemic therapies for the treatment and prevention of breast cancer.- Language was added to allow for the use of hematopoietic growth factors for primary prophylaxis as per National Comprehensive Cancer Network (NCCN)/European Society for Medical Oncology (ESMO) guidelines at the investigator's discretion for patients in the TCH + P arm, and to allow for the use of hematopoietic growth factors for secondary prophylaxis for participants in either treatment arm.- For participants in the T-DM1 + P arm who receive optional adjuvant chemotherapy, language was included to prohibit treatment with trastuzumab in conjunction with anthracyclines.- Language was added to clarify that any participant diagnosed with drug related interstitial lung disease/pneumonitis must discontinue treatment with trastuzumab |
| 06 July 2015 | <ul style="list-style-type: none">- To ensure integrity of the benefit-risk assessment in light of evolving data, language regarding the optional adjuvant chemotherapy for participants in the T-DM1 + P arm was updated from stating that adjuvant chemotherapy was allowed, to recommending adjuvant chemotherapy for participants in the T-DM1 + P arm. Clarification was added regarding participants for whom chemotherapy was recommended, including participants who did not achieve tpCR, and had residual tumor less than (>) 1 centimeter (cm) and/or had residual nodal disease.- Language was updated to recommend the use of hematopoietic growth factors for primary prophylaxis for participants in the TCH + P.- An interim evaluation of total pCR rates by the independent Data Monitoring Committee (iDMC) was specified to be performed to further ensure maintenance of a favorable benefit-risk profile.- Language regarding patient-reported outcomes (PROs) was updated to further specify key treatment-related symptoms and the treatment impact for participants with early breast cancer (EBC). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The reported results are interim only.

Notes: