# Clinical trial results:
# An Open-label, Multi-center Phase I/II Study of the Safety And Tolerability of the Combination of Trastuzumab-MCC-DM1 (T-DM1) with Docetaxel, and Potentially Pertuzumab, for Treatment for Patients with Advanced Breast Cancer

## Summary

| | |
|---|---|
| EudraCT number | 2009-010000-28 |
| Trial protocol | GB FR |
| Global end of trial date | 24 October 2013 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 March 2016 |
| First version publication date | 04 March 2016 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BP22572 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00934856 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +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 | Final |
| Date of interim/final analysis | 24 October 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This was an open-label, multicenter, non-randomized study of the safety and tolerability of combination of trastuzumab emtansine (T-DM1) plus docetaxel for the treatment of participants with metastatic breast cancer (MBC) and of T-DM1 plus docetaxel with/without pertuzumab for the treatment of participants with locally advanced breast cancer (LABC).

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol. The investigator, or a person designated by the investigator obtained written informed consent from each participant participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For participants not qualified or incapable of giving legal consent, written consent was obtained from the legally acceptable representative. Approval from the Independent Ethics Committees (IEC) /Institutional Review Board (IRB) was obtained before starting the study. The protocol amendments were prepared by the Sponsor and approved by the IEC/IRB.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 21 July 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 52 |
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Country: Number of subjects enrolled | France: 21 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 98 |
| EEA total number of subjects | 85 |

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) | 88 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Overall 152 participants were screened, of which 98 participants were enrolled (25 participants with MBC and 73 participants with LABC) and included in the study.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) |

Arm description:

Participants received docetaxel (Doc) 75 milligram per square meter (mg/m^2) administered intravenously on Day 1 and T-DM1 2.4 milligrams per kilogram (mg/kg) administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 75 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | T-DM1 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

T-DM1 was administered intravenously on Day 1 or Day 2 of each 3-week cycle.

| | |
|---|---|
| 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 was administered on Day 1 of each 3-week cycle.

| | |
|---|---|
| **Arm title** | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) |

Arm description:

Participants received docetaxel 60 mg/m^2 administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | T-DM1 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

T-DM1 was administered intravenously on Day 1 or Day 2 of each 3-week cycle.

| | |
|---|---|
| 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 was administered on Day 1 of each 3-week cycle.

| | |
|---|---|
| **Arm title** | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) |

Arm description:

Participants received docetaxel 60 mg/m^2 administered intravenously and T-DM1 2.4 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | T-DM1 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

T-DM1 was administered intravenously on Day 1 or Day 2 of each 3-week cycle.

| | |
|---|---|
| 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 was administered on Day 1 of each 3-week cycle.

| | |
|---|---|
| **Arm title** | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) |

Arm description:

Participants received docetaxel 60 mg/m^2 administered intravenously and T-DM1 3.6 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 3.6 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | T-DM1 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

T-DM1 was administered intravenously on Day 1 or Day 2 of each 3-week cycle.

| | |
|---|---|
| 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 was administered on Day 1 of each 3-week cycle.

| **Arm title** | LABC: T-DM1 + Doc (Doublet Regimen) |
|---|---|

Arm description:

Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 60/75/100 mg/m^2 administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | T-DM1 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

T-DM1 was administered intravenously on Day 1 or Day 2 of each 3-week cycle.

| 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 was administered on Day 1 of each 3-week cycle.

| **Arm title** | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) |
|---|---|

Arm description:

Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 60/75 mg/m^2 administered intravenously, and pertuzumab 840 mg (for Cycle 1) or 420 mg (for remaining cycles) on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | T-DM1 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

T-DM1 was administered intravenously on Day 1 or Day 2 of each 3-week cycle.

| 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 was administered on Day 1 of each 3-week cycle.

| Investigational medicinal product name | Pertuzumab |
|---|---|
| Investigational medicinal product code | |
| Other name | |

| | |
|---|---|
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Pertuzumab at a loading dose of 840 mg intravenous on Day 1, Cycle 1, followed by 420 mg of each 3-week cycle.

| **Number of subjects in period 1** | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) |
|---|---|---|---|
| Started | 6 | 6 | 3 |
| Completed | 1 | 1 | 0 |
| Not completed | 5 | 5 | 3 |
| Physician decision | - | - | 1 |
| Subject Withdrawal | - | - | - |
| Non-compliance with drug | - | - | - |
| Adverse event | 1 | 1 | - |
| Progressive disease | 4 | 4 | 2 |

| **Number of subjects in period 1** | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) | LABC: T-DM1 + Doc (Doublet Regimen) | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) |
|---|---|---|---|
| Started | 10 | 40 | 33 |
| Completed | 3 | 36 | 25 |
| Not completed | 7 | 4 | 8 |
| Physician decision | - | - | - |
| Subject Withdrawal | 1 | - | 1 |
| Non-compliance with drug | - | - | 1 |
| Adverse event | 2 | 4 | 6 |
| Progressive disease | 4 | - | - |

## Baseline characteristics

### Reporting groups

| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) |
|---|---|

Reporting group description:

Participants received docetaxel (Doc) 75 milligram per square meter (mg/m^2) administered intravenously on Day 1 and T-DM1 2.4 milligrams per kilogram (mg/kg) administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 75 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) |
|---|---|

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) |
|---|---|

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously and T-DM1 2.4 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| Reporting group title | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) |
|---|---|

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously and T-DM1 3.6 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 3.6 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| Reporting group title | LABC: T-DM1 + Doc (Doublet Regimen) |
|---|---|

Reporting group description:

Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 60/75/100 mg/m^2 administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| Reporting group title | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) |
|---|---|

Reporting group description:

Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 60/75 mg/m^2 administered intravenously, and pertuzumab 840 mg (for Cycle 1) or 420 mg (for remaining cycles) on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| Reporting group values | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) |
|---|---|---|---|
| Number of subjects | 6 | 6 | 3 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 43 | 50.7 | 57 |
| standard deviation | ± 7.16 | ± 4.84 | ± 12.12 |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 6 | 3 |
| Male | 0 | 0 | 0 |

| **Reporting group values** | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) | LABC: T-DM1 + Doc (Doublet Regimen) | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) |
|---|---|---|---|
| Number of subjects | 10 | 40 | 33 |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 48 | 48.6 | 54.2 |
| standard deviation | ± 9.39 | ± 9.73 | ± 11.43 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 10 | 40 | 33 |
| Male | 0 | 0 | 0 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 98 | | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 98 | | |
| Male | 0 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) |

Reporting group description:

Participants received docetaxel (Doc) 75 milligram per square meter (mg/m^2) administered intravenously on Day 1 and T-DM1 2.4 milligrams per kilogram (mg/kg) administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 75 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) |

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) |

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously and T-DM1 2.4 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Reporting group title | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) |

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously and T-DM1 3.6 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 3.6 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Reporting group title | LABC: T-DM1 + Doc (Doublet Regimen) |

Reporting group description:

Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 60/75/100 mg/m^2 administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| | |
|---|---|
| Reporting group title | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) |

Reporting group description:

Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 60/75 mg/m^2 administered intravenously, and pertuzumab 840 mg (for Cycle 1) or 420 mg (for remaining cycles) on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| | |
|---|---|
| Subject analysis set title | LABC: T-DM1 3.6 mg/kg + Doc 100 mg/m^2 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 100 mg/m^2 administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| | |
|---|---|
| Subject analysis set title | LABC: T-DM1 3.6 mg/kg + Doc 75 mg/m^2 +Pertuzumab 420 mg |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 75 mg/m^2 administered intravenously, and pertuzumab 420 mg on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| | |
|---|---|
| Subject analysis set title | Overall MBC Participants |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This analysis set included participants enrolled in the MBC part of the study.

| Subject analysis set title | Overall MBC and LABC Participants |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

This analysis set included all participants enrolled in the study.

| Subject analysis set title | MBC: T-DM1 2.4 mg/kg |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This analysis set included all MBC participants who received T-DM1 2.4 mg/kg administered intravenously.

| Subject analysis set title | MBC: T-DM1 3.6 mg/kg |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This analysis set included all MBC participants who received T-DM1 3.6 mg/kg administered intravenously.

| Subject analysis set title | LABC: T-DM1 3.6 mg/kg |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This analysis set included all LABC participants who received T-DM1 3.6 mg/kg administered intravenously.

| Subject analysis set title | MBC: Docetaxel 75 mg/m^2 |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This analysis set included all MBC participants who received docetaxel 75 mg/m^2 administered intravenously.

| Subject analysis set title | MBC: Docetaxel 60 mg/m^2 |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This analysis set included all MBC participants who received docetaxel 60 mg/m^2 administered intravenously.

| Subject analysis set title | LABC: Docetaxel 60 mg/m^2 |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This analysis set included all LABC participants who received docetaxel 60 mg/m^2 administered intravenously.

| Subject analysis set title | LABC: Docetaxel 75 mg/m^2 |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This analysis set included all LABC participants who received docetaxel 75 mg/m^2 administered intravenously.

| Subject analysis set title | LABC: Docetaxel 100 mg/m^2 |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This analysis set included all LABC participants who received docetaxel 100 mg/m^2 administered intravenously.

## Primary: Percentage of Participants with Adverse Events (AEs) or Serious AEs (SAEs) – MBC and LABC Population

| End point title | Percentage of Participants with Adverse Events (AEs) or Serious AEs (SAEs) – MBC and LABC Population[1] |
|---|---|

End point description:

AE is any new untoward medical occurrence or worsening of a pre-existing medical condition which does not necessarily have a causal relationship with this treatment. SAE is any untoward medical occurrence

that at any dose results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, results in development of drug dependency or drug abuse, is an important medical event.
Analysis population (AP): All participants who received at least one dose of study medication.

| End point type | Primary |
|---|---|

End point timeframe:

Up to 28 days after last dose for MBC participants and for LABC participants who could not undergo surgery, and up to 6 weeks post-surgery for LABC participants who underwent surgery (maximum up to approximately 3 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was of an explorative nature; therefore only descriptive and exploratory statistical methods were applied, and no statistical hypothesis testing was carried out.

| **End point values** | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 6 | 3 | 10 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| AEs | 100 | 100 | 100 | 100 |
| SAEs | 33.3 | 33.3 | 66.7 | 40 |

| **End point values** | LABC: T-DM1 + Doc (Doublet Regimen) | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 33 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| AEs | 100 | 100 | | |
| SAEs | 22.5 | 27.3 | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Dose Limiting Toxicity (DLT) - MBC and LABC Feasibility Population

| End point title | Number of Participants with Dose Limiting Toxicity (DLT) - MBC and LABC Feasibility Population[2][3] |
|---|---|

End point description:

DLTs included (as per NCI CTCAE grading): Grade 4 thrombocytopenia, thrombocytopenia of any grade with concurrent hemorrhage or requiring blood platelet transfusion, or thrombocytopenia not recovered by Day 21 to at least 100,000/microliter (mcL); Grade 4 neutropenia lasting for more than 7 days;

Febrile neutropenia; Grade greater than or equal to (>/=) 3 neurotoxicity in the form of peripheral neuropathy or peripheral neurotoxicity not improving to baseline or Grade less than or equal to (</=) 1 at Day 21; Any non-hematological toxicity of Grade >/= 3 except for alopecia, fever, and chills, not improving to baseline or Grade </=1 at Day 21, despite adequate toxicity management; Any subjective intolerable toxicity felt by the investigator to be related to either study treatment; Any other treatment-related toxicity prohibiting the start of the Cycle 2 on Day 22; Fulminant skin rash.
AP: All participants who received at least one dose of study medication.

| End point type | Primary |
|---|---|

End point timeframe:

Up to 21 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was of an explorative nature; therefore only descriptive and exploratory statistical methods were applied, and no statistical hypothesis testing was carried out.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Dose limiting toxicities were reported only in the MBC and LABC feasibility part of the study.

| **End point values** | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 6 | 3 | 6 |
| Units: participants | | | | |
| number (not applicable) | 2 | 1 | 0 | 1 |

| **End point values** | LABC: T-DM1 3.6 mg/kg + Doc 100 mg/m^2 | LABC: T-DM1 3.6 mg/kg + Doc 75 mg/m^2 +Pertuzumab 420 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 9 | | |
| Units: participants | | | | |
| number (not applicable) | 2 | 2 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Progression-Free Survival (PFS) – MBC Population

| End point title | Percentage of Participants with Progression-Free Survival (PFS) – MBC Population |
|---|---|

End point description:

PFS was defined as the time interval between the date of the start of treatment and the date of first documentation of progressive disease (PD) or death from any cause, whichever occurred first. Response was based on Response Evaluation Criteria in Solid Tumors (RECIST) Version (V) 1.0. For target lesions

(TLs), PD was at least a 20 percent (%) increase in the sum of longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more lesions. For non-target lesions (NTLs), PD was the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Data for participants without PD or death was censored at the time of the last response assessment. Percentage of participants with PFS was calculated as the (number of participants with PFS) divided by (total number of participants), and then multiplied by 100.
AP: All participants who received at least one dose of study medication.

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

End point timeframe:

Baseline until disease progression or death (up to 33.5 months)

| **End point values** | Overall MBC Participants | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 25 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 60 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: PFS – MBC Population

| End point title | PFS – MBC Population |
|---|---|

End point description:

PFS was defined as the time interval between the date of the start of treatment and the date of first documentation of PD or death from any cause, whichever occurred first. Response was based on RECIST V 1.0. For TLs, PD was at least a 20 % increase in the sum of LD of TLs, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more lesions. For NTLs, PD was the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Data for participants without PD or death was censored at the time of the last response assessment.
AP: All participants who received at least one dose of study medication. A total of 9 participants were censored for PFS analysis.

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

End point timeframe:

Baseline until disease progression or death (up to 33.5 months)

| **End point values** | Overall MBC Participants | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 25 | | | |
| Units: months | | | | |
| median (full range (min-max)) | 13.8 (1.6 to 33.5) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) - MBC Population

| End point title | Percentage of Participants with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) - MBC Population |
|---|---|

End point description:

BOR was defined as CR or PR recorded from baseline until disease progression/recurrence according to RECIST V 1.0 criteria. For TLs, CR was defined as the disappearance of all TLs, and PR was defined as at least a 30% decrease in the sum of LDs of the TLs, taking as a reference the BL sum of LDs. For NTLs, CR was defined as the disappearance of all NTLs and normalization of tumor marker levels. Percentage of participants with BOR rate was calculated as the (number of participants with CR or PR) divided by (total number of participants), and then multiplied by 100. The 95% confidence interval (CI) was determined using the Pearson-Clopper method.
AP: All participants who received at least one dose of study medication.

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

End point timeframe:

Baseline until PD or recurrence (up to 33.5 months)

| End point values | Overall MBC Participants | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 25 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 80 (59.3 to 93.2) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Treatment Failure - MBC Population

| End point title | Percentage of Participants with Treatment Failure - MBC Population |
|---|---|

End point description:

Treatment failure was defined as the discontinuation of treatment for any reason, including the following qualifying events: PD, death from any cause, withdrawal from study treatment, or initiation of non-protocol anti-cancer therapy. Percentage of participants with treatment failure was calculated as the (number of participants with treatment failure) divided by (total number of participants), and then multiplied by 100.
AP: All participants who received at least one dose of study medication.

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

End point timeframe:

Baseline until end of treatment (up to 39.8 months)

| End point values | Overall MBC Participants | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 25 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 64 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Treatment Failure (TTF) - MBC Population

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

End point description:

TTF was defined as the time interval between the date of start of treatment and the date of PD, death from any cause, withdrawal from study treatment, or initiation of non-protocol anti-cancer therapy, whichever occurred first. Participants without an event at the time of the analysis were censored at the date of the last follow-up assessment. Median TTF was estimated using the Kaplan-Meier method.
AP: All participants who received at least one dose of study medication. A total of 9 participants were censored for analysis.

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

End point timeframe:

Baseline until end of treatment (up to 39.8 months)

| End point values | Overall MBC Participants | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 25 | | | |
| Units: months | | | | |
| median (full range (min-max)) | 13.8 (1.4 to 39.8) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with CR or PR or Stable Disease (SD) for at Least 6 months [Clinical Benefit Rate (CBR)] - MBC Population

| End point title | Percentage of Participants with CR or PR or Stable Disease (SD) for at Least 6 months [Clinical Benefit Rate (CBR)] - MBC Population |
|---|---|

End point description:

CBR was defined as % of participants experiencing SD of at least 6 months from the start of treatment plus CR or PR according to the RECIST V 1.0 criteria. For TLs: CR- disappearance of all TLs. PR- at least 30% decrease in the sum of LDs of the TLs, taking as a reference the BL sum of LDs. PD- at least 20% increase in the sum of LD of TLs, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more lesions. SD- neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. For NTLs: CR- disappearance of all NTLs and normalization of tumor

marker levels. SD- persistence of one or more NTLs and/or maintenance of tumor marker level above the normal limits. % of participants= number of participants with CR/PR/SD divided by total number of participants, and then multiplied by 100. 95% CI was determined using the Pearson-Clopper method.
AP: All participants who received at least one dose of study medication.

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

End point timeframe:

Baseline until PD, recurrence or death (up to 33.5 months)

| **End point values** | Overall MBC Participants | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 25 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 92 (74 to 99) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response – MBC Population

| End point title | Duration of Response – MBC Population |
|---|---|

End point description:

Duration of response was calculated for participants whose best overall response was CR or PR based on the RECIST V 1.0 criteria. Duration of response was defined as the time interval between the date the CR or PR was first recorded and the date on which PD was first noted or date of death, whichever occured first. Participants with no documented PD after CR or PR were censored at the last date at which they were known to have had the CR or PR, respectively. Median duration of response was estimated using the Kaplan-Meier method.
AP: All participants who received at least one dose of study medication. A total of 7 participants were censored for analysis.

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

End point timeframe:

Baseline until PD, recurrence or death (up to 32.7 months)

| **End point values** | Overall MBC Participants | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 25 | | | |
| Units: months | | | | |
| median (full range (min-max)) | 12.4 (3.9 to 32.7) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Pathological CR (pCR) – LABC Population

| End point title | Percentage of Participants with Pathological CR (pCR) – LABC Population[4] |
|---|---|

End point description:

The pCR rate was defined as the rate of absence of invasive neoplastic cells at microscopic examination of the tumor remnants and lymph nodes after surgery following primary systemic therapy.
AP: All participants who received at least one dose of study medication.

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

End point timeframe:

Within 6 weeks of post-surgery (up to approximately 3 years)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: pCR was reported only in the LABC part of the study.

| **End point values** | LABC: T-DM1 + Doc (Doublet Regimen) | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 33 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 60 (43.3 to 75.1) | 60.6 (42.1 to 77.1) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with a BOR of CR or PR – LABC Population

| End point title | Percentage of Participants with a BOR of CR or PR – LABC Population[5] |
|---|---|

End point description:

BOR was defined as CR or PR recorded from baseline until disease progression/recurrence according to RECIST V 1.0 criteria. For TLs, CR was defined as the disappearance of all TLs, and PR was defined as at least a 30% decrease in the sum of LDs of the TLs, taking as a reference the baseline (BL) sum of LDs. For NTLs, CR was defined as the disappearance of all NTLs and normalization of tumor marker levels. Percentage of participants with BOR rate was calculated as the (number of participants with CR or PR) divided by (total number of participants), and then multiplied by 100. The 95% CI was determined using the Pearson-Clopper method.
AP: All participants who received at least one dose of study medication.

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

End point timeframe:

Baseline until PD, recurrence or death (up to approximately 3 years)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: BOR of CR or PR was reported only in the LABC part of the study.

| End point values | LABC: T-DM1 + Doc (Doublet Regimen) | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 33 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 70 (53.5 to 83.4) | 51.5 (33.5 to 69.2) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Anti-Therapeutic Antibody Response at Baseline and Post-Trazustumab Emtansine Dosing - MBC and LABC Population

| End point title | Percentage of Participants With Anti-Therapeutic Antibody Response at Baseline and Post-Trazustumab Emtansine Dosing - MBC and LABC Population |
|---|---|

End point description:

Percentage of participants with Human Anti-human Antibody response was reported.
AP: All participants who received at least one dose of study medication.

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

End point timeframe:

Baseline and post-dose (up to approximately 3 years)

| End point values | Overall MBC and LABC Participants | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 98 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Baseline, positive and post-dose, positive | 2 | | | |
| Baseline, positive and post-dose, negative | 1 | | | |
| Baseline, positive and post-dose, missing | 0 | | | |
| Baseline, negative and post-dose, positive | 1 | | | |
| Baseline, negative and post-dose, negative | 69 | | | |
| Baseline, negative and post-dose, missing | 17 | | | |
| Baseline, missing and post-dose, positive | 0 | | | |
| Baseline, missing and post-dose, negative | 7 | | | |
| Baseline, missing and post-dose, missing | 2 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Concentration (Cmax) of Serum Trastuzumab Emtansine – MBC and LABC Population

| End point title | Maximum Observed Concentration (Cmax) of Serum Trastuzumab Emtansine – MBC and LABC Population |
|---|---|

End point description:

Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1, Day 8)

| End point values | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 10 | 73 | |
| Units: micrograms per milliliter (mcg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 10, 73) | 78.6 (± 16.6) | 76.2 (± 36.4) | 85.7 (± 15.3) | |
| Cycle 2 (n= 14, 9, 67) | 78.7 (± 16.7) | 93.7 (± 27.6) | 80.2 (± 18.4) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent Terminal Half-Life (t1/2) of Serum Trastuzumab Emtansine – MBC and LABC Population

| End point title | Apparent Terminal Half-Life (t1/2) of Serum Trastuzumab Emtansine – MBC and LABC Population |
|---|---|

End point description:

t1/2 was calculated as per 'natural logarithm of 2 [ln(2)]/λz' formula, and λz was the terminal rate constant. λz reflects the speed of drug elimination invivo (within the living), and was obtained from linear regression of the log-transformed terminal part of the concentration-time curve.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who

received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| **End point values** | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 8 | 72 | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 7, 72) | 2.79 (± 0.637) | 3.45 (± 0.779) | 3.46 (± 0.558) | |
| Cycle 2 (n= 14, 8, 63) | 3.14 (± 0.574) | 3.85 (± 0.568) | 3.62 (± 0.516) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: AUCinf of Serum Trastuzumab Emtansine – MBC and LABC Population

| End point title | AUCinf of Serum Trastuzumab Emtansine – MBC and LABC Population |
|---|---|

End point description:

AUCinf is defined as the area under the serum concentration-time curve (AUC) from time 0 extrapolated to infinity.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| **End point values** | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 8 | 72 | |
| Units: day*mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 7, 72) | 396 (± 124) | 447 (± 144) | 442 (± 90.7) | |
| Cycle 2 (n= 14, 8, 63) | 471 (± 94.5) | 556 (± 223) | 488 (± 123) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Clearence (CL) of Serum Trastuzumab Emtansine – MBC and LABC Population

| End point title | Clearence (CL) of Serum Trastuzumab Emtansine – MBC and LABC Population |
|---|---|

End point description:

CL was estimated as dose divided by AUCinf.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| End point values | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 8 | 72 | |
| Units: milliliter/day/kilogram (mL/day/kg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 7, 72) | 8.94 (± 12) | 8.87 (± 2.96) | 8.48 (± 1.86) | |
| Cycle 2 (n= 14, 8, 63) | 5.21 (± 1.27) | 7.16 (± 2.95) | 7.68 (± 2.73) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Vss of Serum Trastuzumab Emtansine – MBC and LABC Population

| End point title | Vss of Serum Trastuzumab Emtansine – MBC and LABC Population |
|---|---|

End point description:

Vss is defined as the volume of distribution at steady state.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1, Day 8)

| **End point values** | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 8 | 72 | |
| Units: mL/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 7, 72) | 22.1 (± 6.74) | 33.2 (± 9.13) | 33.2 (± 8.36) | |
| Cycle 2 (n= 14, 8, 63) | 17.7 (± 4.73) | 31.4 (± 16.9) | 28.8 (± 9.32) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax of Total Serum Trastuzumab – MBC and LABC Population

| End point title | Cmax of Total Serum Trastuzumab – MBC and LABC Population |
|---|---|

End point description:

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| **End point values** | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 10 | 73 | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 10, 73) | 88.7 (± 22.6) | 89.2 (± 47.4) | 120 (± 46.6) | |
| Cycle 2 (n= 14, 9, 67) | 85.8 (± 17.5) | 97.7 (± 29.4) | 113 (± 43.8) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: T1/2 of Total Serum Trastuzumab – MBC and LABC Population

| End point title | T1/2 of Total Serum Trastuzumab – MBC and LABC Population |
|---|---|

End point description:

t1/2 was calculated as per 'natural logarithm of 2 [ln(2)]/λz' formula, and λz was the terminal rate constant. λz reflects the speed of drug elimination invivo (within the living), and was obtained from linear regression of the log-transformed terminal part of the concentration-time curve.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| **End point values** | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 8 | 73 | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 7, 73) | 6.44 (± 2.6) | 6.38 (± 1.41) | 8.12 (± 4.2) | |
| Cycle 2 (n= 13, 8, 62) | 6.67 (± 1.92) | 7.83 (± 1.68) | 9.91 (± 5.01) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: AUCinf of Total Serum Trastuzumab – MBC and LABC Population

| End point title | AUCinf of Total Serum Trastuzumab – MBC and LABC Population |
|---|---|

End point description:

AUCinf is defined as the AUC from time 0 extrapolated to infinity.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| End point values | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 8 | 73 | |
| Units: day*mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 7, 73) | 785 (± 429) | 707 (± 201) | 1210 (± 856) | |
| Cycle 2 (n= 13, 8, 62) | 809 (± 308) | 1040 (± 359) | 1570 (± 1180) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: CL of Total Serum Trastuzumab – MBC and LABC Population

| End point title | CL of Total Serum Trastuzumab – MBC and LABC Population |
|---|---|

End point description:

CL was estimated as dose divided by AUCinf.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| End point values | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 8 | 73 | |
| Units: mL/day/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 7, 73) | 6.78 (± 13.3) | 5.45 (± 1.46) | 4.22 (± 2.13) | |
| Cycle 2 (n= 13, 8, 62) | 3.32 (± 1.53) | 3.71 (± 1.23) | 3.38 (± 2.11) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vss of Total Serum Trastuzumab – MBC and LABC Population

| End point title | Vss of Total Serum Trastuzumab – MBC and LABC Population |
|---|---|

End point description:

Vss is defined as the volume of distribution at steady state.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| **End point values** | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 8 | 73 | |
| Units: mL/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 15, 7, 73) | 27 (± 7.16) | 41.3 (± 9.24) | 36.5 (± 12.7) | |
| Cycle 2 (n= 13, 8, 62) | 24.6 (± 5.05) | 36.4 (± 11.3) | 35.2 (± 12) | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Cmax of Plasma DM1 – MBC and LABC Population

| End point title | Cmax of Plasma DM1 – MBC and LABC Population |
|---|---|

End point description:

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| **End point values** | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 13 | 9 | 73 | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 13, 9, 73) | 3.55 (± 1.6) | 3.42 (± 0.944) | 4.51 (± 1.38) | |
| Cycle 2 (n= 13, 9, 67) | 3.34 (± 0.815) | 3.9 (± 1.19) | 4.65 (± 1.57) | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: T1/2 of Plasma DM1 – MBC and LABC Population

| End point title | T1/2 of Plasma DM1 – MBC and LABC Population |
|---|---|

End point description:

t1/2 was calculated as per 'natural logarithm of 2 [ln(2)]/λz' formula, and λz was the terminal rate constant. λz reflects the speed of drug elimination invivo (within the living), and was obtained from linear regression of the log-transformed terminal part of the concentration-time curve.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.
'99999' signifies that SD was not calculable due to only 1 participant available for PK analysis.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| End point values | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12 | 7 | 68 | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 12, 7, 68) | 1.12 (± 0.702) | 1.2 (± 0.985) | 1.87 (± 1.63) | |
| Cycle 2 (n= 2, 1, 31) | 3.75 (± 0.912) | 2.91 (± 99999) | 3.32 (± 0.7) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: AUCinf of Plasma DM1 – MBC and LABC Population

| End point title | AUCinf of Plasma DM1 – MBC and LABC Population |
|---|---|

End point description:

AUCinf is the area under the serum concentration-time curve from time 0 extrapolated to infinity. Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.
'99999' signifies that SD was not calculable due to only 1 participant available for PK analysis.

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

End point timeframe:

Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)

| End point values | MBC: T-DM1 2.4 mg/kg | MBC: T-DM1 3.6 mg/kg | LABC: T-DM1 3.6 mg/kg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12 | 7 | 68 | |
| Units: day*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 12, 7, 68) | 5.72 (± 5.16) | 5.01 (± 2.54) | 9.38 (± 9.33) | |
| Cycle 2 (n= 2, 1, 31) | 17.8 (± 4.6) | 20 (± 99999) | 18.5 (± 4.28) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax of Docetaxel – MBC and LABC Population

| End point title | Cmax of Docetaxel – MBC and LABC Population |
|---|---|

End point description:

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of docetaxel with at least one post-dose concentration data point.

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

End point timeframe:

Day 1, Cycle 1, (pre-dose, at 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion), Day 1, Cycle 2 (pre-dose, at 30 minutes and 59 minutes after the start of infusion), and 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion

| End point values | MBC: Docetaxel 75 mg/m^2 | MBC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 75 mg/m^2 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 19 | 14 | 36 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 500 (± 216) | 1300 (± 829) | 1470 (± 551) | 1710 (± 426) |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 791 (± 637) | 1320 (± 826) | 1590 (± 441) | 1960 (± 552) |

| End point values | LABC: Docetaxel 100 mg/m^2 | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 22 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 2950 (± 1540) | | | |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 2790 (± 979) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: T1/2 of Docetaxel – MBC and LABC Population

| End point title | T1/2 of Docetaxel – MBC and LABC Population |
|---|---|

End point description:

t1/2 was calculated as per 'natural logarithm of 2 [ln(2)]/λz' formula, and λz was the terminal rate constant. λz reflects the speed of drug elimination invivo (within the living), and was obtained from linear regression of the log-transformed terminal part of the concentration-time curve.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of docetaxel with at least one post-dose concentration data point.

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

End point timeframe:

Day 1, Cycle 1, (pre-dose, at 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion), Day 1, Cycle 2 (pre-dose, at 30 minutes and 59 minutes after the start of infusion), and 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion

| **End point values** | MBC: Docetaxel 75 mg/m^2 | MBC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 75 mg/m^2 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 19 | 14 | 36 |
| Units: hours (hr) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 6.83 (± 4.22) | 5.17 (± 4.02) | 4.25 (± 5.61) | 8.29 (± 5.75) |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 7.7 (± 4.15) | 7.88 (± 6.18) | 5.9 (± 3.83) | 6.69 (± 5.55) |

| **End point values** | LABC: Docetaxel 100 mg/m^2 | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 22 | | | |
| Units: hours (hr) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 8.76 (± 3.82) | | | |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 7.24 (± 3.58) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: AUCinf of Docetaxel – MBC and LABC Population

| End point title | AUCinf of Docetaxel – MBC and LABC Population |
|---|---|

End point description:

AUCinf is the AUC from time 0 extrapolated to infinity.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of docetaxel with at least one post-dose concentration data point.

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

End point timeframe:

Day 1, Cycle 1, (pre-dose, at 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion), Day 1, Cycle 2 (pre-dose, at 30 minutes and 59 minutes after the start of infusion), and 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion

| End point values | MBC: Docetaxel 75 mg/m^2 | MBC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 75 mg/m^2 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 19 | 14 | 36 |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 1050 (± 475) | 1560 (± 874) | 1540 (± 421) | 2140 (± 669) |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 1700 (± 1190) | 1710 (± 875) | 3260 (± 5100) | 2420 (± 887) |

| End point values | LABC: Docetaxel 100 mg/m^2 | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 22 | | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 4020 (± 2120) | | | |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 3840 (± 1930) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: CL of Docetaxel – MBC and LABC Population

| End point title | CL of Docetaxel – MBC and LABC Population |
|---|---|

End point description:

CL was estimated as dose divided by AUCinf.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of docetaxel with at least one post-dose concentration data point.

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

End point timeframe:

Day 1, Cycle 1, (pre-dose, at 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion), Day 1, Cycle 2 (pre-dose, at 30 minutes and 59 minutes after the start of infusion), and 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion

| End point values | MBC: Docetaxel 75 mg/m^2 | MBC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 75 mg/m^2 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 19 | 14 | 36 |
| Units: L/hr/m^2 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 82.2 (± 32.6) | 58.3 (± 40.9) | 42.8 (± 16.4) | 39.5 (± 16.8) |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 59 (± 29.9) | 51.2 (± 38.5) | 32.6 (± 13.1) | 33.6 (± 11.9) |

| End point values | LABC: Docetaxel 100 mg/m^2 | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 22 | | | |
| Units: L/hr/m^2 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 30.5 (± 14.5) | | | |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 27.9 (± 9.13) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Vss of Docetaxel – MBC and LABC Population

| End point title | Vss of Docetaxel – MBC and LABC Population |
|---|---|

End point description:

Vss is defined as the volume of distribution at steady state.
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of docetaxel with at least one post-dose concentration data point.

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

End point timeframe:

Day 1, Cycle 1, (pre-dose, at 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion), Day 1, Cycle 2 (pre- dose, at 30 minutes and 59 minutes after the start of infusion), and 15 and 30 minutes, 1, 2, 4, 8 and 23 hours after end of infusion

| **End point values** | MBC: Docetaxel 75 mg/m^2 | MBC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 60 mg/m^2 | LABC: Docetaxel 75 mg/m^2 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 19 | 14 | 36 |
| Units: L/m^2 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 530 (± 398) | 203 (± 275) | 75 (± 113) | 126 (± 86.7) |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 380 (± 257) | 253 (± 234) | 93.2 (± 64.7) | 79 (± 53.6) |

| **End point values** | LABC: Docetaxel 100 mg/m^2 | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 22 | | | |
| Units: L/m^2 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n= 6, 19, 14, 36, 22) | 116 (± 73.3) | | | |
| Cycle 2 (n= 6, 17, 12, 35, 19) | 84.8 (± 39.1) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 28 days after last dose for MBC participants and for LABC participants who could not undergo surgery, and up to 6 weeks post-surgery for LABC participants who underwent surgery (maximum up to approximately 3 years)

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) |

Reporting group description:

Participants received docetaxel 75 mg/m^2 administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 75 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) |

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cy,cles, docetaxel 60 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent

| | |
|---|---|
| Reporting group title | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) |

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously and T-DM1 2.4 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

| | |
|---|---|
| Reporting group title | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) |

Reporting group description:

Participants received docetaxel 60 mg/m^2 administered intravenously and T-DM1 3.6 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m^2 was stopped and T-DM1 3.6 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity or withdrawal of participant consent.

| | |
|---|---|
| Reporting group title | LABC: T-DM1 + Doc (Doublet Regimen) |

Reporting group description:

Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 60/75/100 mg/m^2 administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| | |
|---|---|
| Reporting group title | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) |

Reporting group description:

Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 60/75 mg/m^2 administered intravenously, and pertuzumab 840 mg (for Cycle 1) or 420 mg (for remaining cycles) on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

| **Serious adverse events** | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 6 (33.33%) | 2 / 3 (66.67%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device deployment issue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Melanoderma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatitis exfoliative | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatomyositis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) | LABC: T-DM1 + Doc (Doublet Regimen) | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 9 / 40 (22.50%) | 9 / 33 (27.27%) |
| number of deaths (all causes) | 0 | 2 | 0 |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 2 / 33 (6.06%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device deployment issue | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Uterine polyp | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 2 / 33 (6.06%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Melanoderma | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatitis exfoliative | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Dermatomyositis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (over 2 days) | MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m^2 (same day) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 6 / 6 (100.00%) | 3 / 3 (100.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Flushing | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pallor | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Tooth repair | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 5 / 6 (83.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 25 | 26 | 4 |
| Mucosal inflammation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 6 (50.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 4 | 4 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 5 / 6 (83.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 7 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 5 | 1 |
| Mucosal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Local swelling | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Temperature intolerance | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Temperature regulation disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vaccination site reaction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Breast pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Epistaxis | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 5 / 6 (83.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 14 | 20 | 2 |
| Cough | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 2 | 2 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal inflammation | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Increased bronchial secretion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Suffocation feeling | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Recall phenomenon | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tooth avulsion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Systolic dysfunction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 4 | 1 | 4 |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 28 | 6 | 1 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 6 (50.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 3 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysaesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Aphonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Migraine | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Burning sensation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Sinus headache | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 5 / 6 (83.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 39 | 19 | 11 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 4 / 6 (66.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 8 | 7 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 3 / 6 (50.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 17 | 12 | 5 |
| Lymphopenia | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 11 | 6 | 0 |
| Anaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 4 | 1 |
| Conjunctivitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Dry eye | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Xerophthalmia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blepharospasm | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Conjunctival oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Photophobia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dacryostenosis acquired | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eyelids pruritus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 5 / 6 (83.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 18 | 31 | 4 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 6 (50.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 5 | 3 | 1 |
| Constipation | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 3 / 3 (100.00%) |
| occurrences (all) | 1 | 9 | 8 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 4 | 1 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 2 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 4 / 6 (66.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 10 | 8 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 5 | 5 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|---|---|---|---|
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 11 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Aphthous Stomatitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Breath odour | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epulis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth loss | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 8 | 3 | 0 |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 4 / 6 (66.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nail disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nail dystrophy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Blister | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cold sweat | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Madarosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Papule | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pyelocaliectasis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 6 | 4 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 4 / 6 (66.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Musculoskeletal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 0 | 1 |
| Back pain | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 6 | 3 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 24 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 3 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle twitching | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Spinal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 7 | 0 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |

| | | | |
|---|---|---|---|
| Laryngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mastitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 4 | 3 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m^2 (same day) | LABC: T-DM1 + Doc (Doublet Regimen) | LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 10 (100.00%) | 40 / 40 (100.00%) | 33 / 33 (100.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 5 / 40 (12.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Flushing | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|---|---|---|
| Haematoma | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pallor | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Varicose vein | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Surgical and medical procedures | | | |
| Tooth repair | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 10 (60.00%) | 25 / 40 (62.50%) | 20 / 33 (60.61%) |
| occurrences (all) | 32 | 55 | 40 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 20 / 40 (50.00%) | 15 / 33 (45.45%) |
| occurrences (all) | 3 | 27 | 23 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 8 / 40 (20.00%) | 10 / 33 (30.30%) |
| occurrences (all) | 2 | 10 | 11 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 10 / 40 (25.00%) | 9 / 33 (27.27%) |
| occurrences (all) | 1 | 12 | 13 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 3 / 40 (7.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 4 | 3 | 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 4 / 40 (10.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 1 | 1 |
| Mucosal dryness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 1 | 3 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 40 (7.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Local swelling | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Temperature intolerance | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Temperature regulation disorder | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaccination site reaction | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 10 (10.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 5 | 1 |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 40 (10.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 4 | 1 |
| Breast pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 1 | 1 |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 6 / 10 (60.00%) | 21 / 40 (52.50%) | 19 / 33 (57.58%) |
| occurrences (all) | 41 | 28 | 40 |
| Cough | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 4 / 40 (10.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 4 | 5 | 4 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 4 / 40 (10.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 6 | 4 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 2 / 40 (5.00%) | 6 / 33 (18.18%) |
| occurrences (all) | 5 | 2 | 8 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 40 (10.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 6 | 1 |
| Oropharyngeal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 2 / 33 (6.06%) |
| occurrences (all) | 2 | 1 | 2 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 2 | 1 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 2 | 1 |
| Nasal inflammation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Increased bronchial secretion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Suffocation feeling | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 8 / 40 (20.00%) | 6 / 33 (18.18%) |
| occurrences (all) | 3 | 10 | 6 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 3 / 33 (9.09%) |
| occurrences (all) | 1 | 1 | 3 |

| | | | |
|---|---|---|---|
| Depression | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 11 / 40 (27.50%) | 7 / 33 (21.21%) |
| occurrences (all) | 1 | 16 | 16 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 8 / 40 (20.00%) | 4 / 33 (12.12%) |
| occurrences (all) | 1 | 10 | 7 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 40 (7.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laceration | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ligament sprain | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Recall phenomenon | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth avulsion | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Systolic dysfunction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 19 / 40 (47.50%) | 13 / 33 (39.39%) |
| occurrences (all) | 5 | 23 | 16 |
| Headache | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 12 / 40 (30.00%) | 11 / 33 (33.33%) |
| occurrences (all) | 9 | 15 | 16 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 8 / 40 (20.00%) | 5 / 33 (15.15%) |
| occurrences (all) | 3 | 9 | 5 |
| Paraesthesia | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 4 / 40 (10.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 3 | 5 | 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 40 (7.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 3 | 1 |
| Restless legs syndrome | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 40 (10.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 4 | 1 |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Aphonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Migraine | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Burning sensation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus headache | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 7 / 10 (70.00%) | 11 / 40 (27.50%) | 12 / 33 (36.36%) |
| occurrences (all) | 20 | 23 | 15 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 10 (80.00%) | 9 / 40 (22.50%) | 7 / 33 (21.21%) |
| occurrences (all) | 17 | 13 | 8 |

| | | | |
|---|---|---|---|
| Leukopenia | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 3 / 40 (7.50%) | 3 / 33 (9.09%) |
| occurrences (all) | 10 | 3 | 4 |
| Lymphopenia | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 3 / 40 (7.50%) | 4 / 33 (12.12%) |
| occurrences (all) | 8 | 5 | 7 |
| Anaemia | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 4 / 40 (10.00%) | 4 / 33 (12.12%) |
| occurrences (all) | 6 | 4 | 5 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 2 | 1 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vertigo | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 15 / 40 (37.50%) | 16 / 33 (48.48%) |
| occurrences (all) | 6 | 17 | 20 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 6 / 40 (15.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 1 | 7 | 2 |
| Dry eye | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 40 (7.50%) | 5 / 33 (15.15%) |
| occurrences (all) | 1 | 3 | 5 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 6 / 40 (15.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 8 | 2 |
| Xerophthalmia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 2 | 2 |
| Blepharospasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Conjunctival oedema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 4 | 1 |
| Eye disorder | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 40 (7.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Eye pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Photophobia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Dacryostenosis acquired | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelids pruritus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 16 / 40 (40.00%) | 16 / 33 (48.48%) |
| occurrences (all) | 14 | 30 | 25 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 12 / 40 (30.00%) | 18 / 33 (54.55%) |
| occurrences (all) | 3 | 23 | 33 |

| | | | |
|---|---|---|---|
| Constipation | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 19 / 40 (47.50%) | 11 / 33 (33.33%) |
| occurrences (all) | 6 | 21 | 14 |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 14 / 40 (35.00%) | 10 / 33 (30.30%) |
| occurrences (all) | 3 | 18 | 12 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 10 (50.00%) | 11 / 40 (27.50%) | 11 / 33 (33.33%) |
| occurrences (all) | 6 | 13 | 14 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 10 (50.00%) | 4 / 40 (10.00%) | 5 / 33 (15.15%) |
| occurrences (all) | 7 | 4 | 7 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 5 / 40 (12.50%) | 4 / 33 (12.12%) |
| occurrences (all) | 7 | 7 | 4 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 40 (7.50%) | 5 / 33 (15.15%) |
| occurrences (all) | 1 | 3 | 7 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 40 (10.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 4 | 3 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 5 / 40 (12.50%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 8 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 40 (7.50%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 3 | 5 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 40 (10.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 4 | 4 |
| Gingival bleeding | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 3 / 40 (7.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 0 / 40 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 5 | 0 | 2 |

| | | | |
|---|---|---|---|
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 40 (7.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Cheilitis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 1 | 1 |
| Oral pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 3 | 1 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Aphthous Stomatitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Breath odour | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epulis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Tooth loss | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 20 / 40 (50.00%) | 12 / 33 (36.36%) |
| occurrences (all) | 4 | 20 | 12 |
| Rash | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 8 / 40 (20.00%) | 11 / 33 (33.33%) |
| occurrences (all) | 2 | 13 | 15 |
| Nail disorder | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 8 / 40 (20.00%) | 4 / 33 (12.12%) |
| occurrences (all) | 0 | 8 | 4 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 9 / 40 (22.50%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 9 | 3 |
| Nail dystrophy | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 5 / 40 (12.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 2 | 6 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 1 / 40 (2.50%) | 2 / 33 (6.06%) |
| occurrences (all) | 2 | 1 | 2 |
| Erythema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 2 | 2 |
| Eczema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 1 | 2 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 1 | 2 |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 40 (7.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 3 | 2 |
| Onychalgia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 2 | 1 |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 2 | 1 |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Blister | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cold sweat | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Madarosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Papule | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin toxicity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 5 / 33 (15.15%) |
| occurrences (all) | 0 | 1 | 5 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyelocaliectasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 18 / 40 (45.00%) | 8 / 33 (24.24%) |
| occurrences (all) | 1 | 37 | 10 |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 9 / 40 (22.50%) | 3 / 33 (9.09%) |
| occurrences (all) | 8 | 17 | 4 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 10 / 40 (25.00%) | 6 / 33 (18.18%) |
| occurrences (all) | 4 | 16 | 6 |
| Back pain | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 6 / 40 (15.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 7 | 8 | 3 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 6 / 40 (15.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 8 | 3 |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 4 / 40 (10.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 5 | 4 | 3 |
| Musculoskeletal stiffness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 4 | 1 | 1 |
| Muscle twitching | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 2 | 1 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 10 (50.00%) | 7 / 40 (17.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 5 | 9 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 4 / 40 (10.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 3 | 5 | 4 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 4 / 40 (10.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 2 | 4 | 1 |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 2 | 2 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 40 (10.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 4 | 1 |
| Influenza | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 40 (7.50%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 2 | 1 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 40 (5.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 2 | 1 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 1 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 2 | 1 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 1 | 1 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 3 |

| | | | |
|---|---|---|---|
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Mastitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 40 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 9 / 40 (22.50%) | 9 / 33 (27.27%) |
| occurrences (all) | 2 | 11 | 13 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 40 (2.50%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 1 | 2 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 June 2009 | Version B:<br>• Updated blood volume and schedule for PK sampling<br>• Clarified that palliative radiotherapy was allowed for brain metastasis prior to study entry. |
| 26 August 2009 | Version C:<br>Provision of better assessment of early safety parameters, via more intensive hematology and biochemistry assessments in Weeks 1 and 2 of Cycles 1-3. |
| 02 February 2010 | Version D:<br>• Reduction of the maximum dose docetaxel from 100 mg/m^2 to 75 mg/m^2 in first-line participants<br>• Addition of a third Cohort of 3 to 6 participants to receive 2.4 mg/kg T-DM1 + 60 mg/m^2 docetaxel, administered both on Day 1 of each cycle<br>• Addition of Dose Level 4 (T-DM1 3.6 mg/kg and docetaxel 60 mg/m^2 every 3 weeks) and Dose Level 5 (T-DM1 3.0 mg/kg and docetaxel 60 mg/m^2 every 3 weeks) to study design<br>• Updated participants numbers and PK sampling accordingly<br>• Clarification of the DLT criteria regarding "nonhaematological" toxicities and dose modifications for hepatotoxicity/hematologic toxicity<br>• Addition of exclusion criterion regarding alkaline phosphatase. |
| 16 June 2010 | Version E:<br>Permission for participants who had newly developed isolated brain metastases that were treatable with radiation to continue with study treatment until systemic progression. |
| 18 February 2011 | Version F:<br>• Inclusion of participants with newly diagnosed HER2-positive LABC, with option for docetaxel dose escalation<br>• Closure of the feasibility part of the study in MBC<br>• Removal of overall survival and time to tumour progression as secondary endpoints<br>• Removal of censoring for non-protocol therapy from the analysis of PFS<br>• Update of safety guidance with respect to drug-induced liver injury and pregnancy. |
| 31 August 2011 | Version G:<br>Inclusion of addition of pertuzumab to T-DM1 and docetaxel in LABC participants. |
| 11 October 2011 | Version H:<br>Addition of United States sites to the study. |
| 23 February 2012 | Version I:<br>• Increase in participant numbers in extension part for LABC<br>• Revision of hepatotoxicity information. |

| | |
|---|---|
| 13 February 2013 | Version J:<br>Updated safety information for identified risks and adverse events of interest. |

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.

| |
|---|
| None reported. |

Notes: