



Clinical trial results:

Phase I Study of the Combination of Trastuzumab Emtansine (T-DM1) and Capecitabine in HER2-Positive Metastatic Breast Cancer and HER2-Positive Locally Advanced/Metastatic Gastric Cancer Patients, Followed by a Randomized, Open-Label Phase II Study of Trastuzumab Emtansine and Capecitabine versus Trastuzumab Emtansine Alone in HER2-Positive Metastatic Breast Cancer

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2012-001547-46 |
| Trial protocol | ES FR PT SK IT DE GR |
| Global end of trial date | 31 May 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 14 June 2018 |
| First version publication date | 14 June 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | MO28230 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01702558 |
| 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 | 31 May 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 May 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Phase 1: The primary objective was to determine the maximum tolerated dose (MTD) of the combination of trastuzumab emtansine and capecitabine in participants with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC) and locally advanced/metastatic gastric cancer (LA/mGC).

Phase 2: The primary objective was to explore the efficacy of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone in participants with HER2-positive mBC, as measured by overall response rate (ORR) according to Response Evaluation Criteria for Solid Tumors Version 1.1 (RECIST v1.1) per investigator local assessment.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP). Approval from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. No modifications were made to the protocol after receipt of the IEC/IRB approval.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 03 December 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 6 |
| Country: Number of subjects enrolled | Brazil: 10 |
| Country: Number of subjects enrolled | Canada: 12 |
| Country: Number of subjects enrolled | France: 17 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Greece: 16 |
| Country: Number of subjects enrolled | Italy: 24 |
| Country: Number of subjects enrolled | Portugal: 6 |
| Country: Number of subjects enrolled | Russian Federation: 40 |
| Country: Number of subjects enrolled | Serbia: 6 |
| Country: Number of subjects enrolled | Slovakia: 14 |
| Country: Number of subjects enrolled | Spain: 15 |
| Worldwide total number of subjects | 179 |
| EEA total number of subjects | 105 |

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) | 148 |
| From 65 to 84 years | 31 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 234 participants were screened, out of which, 182 participants were enrolled into the study. Out of the 182 enrolled participants, 3 participants were excluded from all safety and efficacy analyses because they did not sign correct Informed Consent Form (ICF).

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape |

Arm description:

In Phase 1, Cohort 1 participants (with mBC) received trastuzumab emtansine (T-DM1) at a dose of 3.6 milligrams per kilogram (mg/kg) via intravenous (IV) infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine (Cape) at a dose level (DL) of 750 milligrams per meter squared (mg/m²) via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, disease progression (PD), death, reasons deemed by the treating physician, or study termination by the sponsor.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | Xeloda |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine was administered at dose level 1 (750 mg/m²) via tablet orally twice daily on Days 1-14 of each 21-day cycle.

| | |
|--|--|
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | Kadcyla, RO5304020 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab emtansine was administered at a dose of 3.6 mg/kg via IV infusion on Day 1 (on Day 2 of Cycle 1) of each 21-day cycle.

| | |
|------------------|--|
| Arm title | Phase 1 (mBC) Cohort 1 (DL -1): T-DM1 + Cape |
|------------------|--|

Arm description:

In Phase 1, Cohort 1 participants (with mBC) received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine at a dose level of 700 mg/m² via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------------|
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | Xeloda |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine was administered at dose level -1 (700 mg/m²) via tablet orally twice daily on Days 1-14 of each 21-day cycle.

| | |
|--|--|
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | Kadcyla, RO5304020 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab emtansine was administered at a dose of 3.6 mg/kg via IV infusion on Day 1 (on Day 2 of Cycle 1) of each 21-day cycle.

| | |
|------------------|---|
| Arm title | Phase 1 (LA/mGC) Cohort 2 (DL -1): T-DM1 + Cape |
|------------------|---|

Arm description:

In Phase 1, Cohort 2 participants (with LA/mGC) received trastuzumab emtansine at a dose of 2.4 mg/kg via IV infusion on Day 1 (Day 2 of first week) of every week along with capecitabine at a dose level of 700 mg/m² via tablet orally twice daily on Days 1-14 followed by a 7-day rest period, in each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | Xeloda |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine was administered at MTD (700 mg/m²) via tablet orally twice daily on Days 1-14 followed by a 7-day rest period.

| | |
|--|--|
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | Kadcyla, RO5304020 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab emtansine was administered at a dose of 2.4 mg/kg via IV infusion on Day 1 (Day 2 of first week) every week.

| | |
|------------------|-----------------------------|
| Arm title | Phase 2 (mBC): T-DM1 + Cape |
|------------------|-----------------------------|

Arm description:

In Phase 2, participants (with mBC) who were randomized to this group received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle along with capecitabine at a dose level of 700 mg/m² via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | Xeloda |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine was administered at MTD (700 mg/m²) via tablet orally twice daily on Days 1-14 of each 21-day cycle.

| | |
|--|--|
| Investigational medicinal product name | Trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | Kadcyla |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab emtansine was administered at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle.

| | |
|------------------|----------------------|
| Arm title | Phase 2 (mBC): T-DM1 |
|------------------|----------------------|

Arm description:

In Phase 2, participants (with mBC) who were randomized to this group received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor.

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

Dosage and administration details:

Trastuzumab emtansine was administered at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle.

| Number of subjects in period 1 | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL -1): T-DM1 + Cape | Phase 1 (LA/mGC) Cohort 2 (DL -1): T-DM1 + Cape |
|---------------------------------------|--|---|--|
| Started | 7 | 5 | 6 |
| Completed | 3 | 1 | 1 |
| Not completed | 4 | 4 | 5 |
| Consent withdrawn by subject | - | - | - |
| Death | 4 | 3 | 3 |
| Safety Follow-Up less than 3 Months | - | - | 2 |
| Unspecified | - | - | - |
| Study Terminated by Sponsor | - | 1 | - |
| Lost to follow-up | - | - | - |

| Number of subjects in period 1 | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 |
|---------------------------------------|-----------------------------|----------------------|
| Started | 81 | 80 |
| Completed | 34 | 38 |
| Not completed | 47 | 42 |
| Consent withdrawn by subject | 12 | 4 |
| Death | 16 | 20 |
| Safety Follow-Up less than 3 Months | - | - |

| | | |
|-----------------------------|----|----|
| Unspecified | 16 | 17 |
| Study Terminated by Sponsor | - | 1 |
| Lost to follow-up | 3 | - |

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape |
| Reporting group description: | |
| In Phase 1, Cohort 1 participants (with mBC) received trastuzumab emtansine (T-DM1) at a dose of 3.6 milligrams per kilogram (mg/kg) via intravenous (IV) infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine (Cape) at a dose level (DL) of 750 milligrams per meter squared (mg/m ²) via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, disease progression (PD), death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Reporting group title | Phase 1 (mBC) Cohort 1 (DL -1): T-DM1 + Cape |
| Reporting group description: | |
| In Phase 1, Cohort 1 participants (with mBC) received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine at a dose level of 700 mg/m ² via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Reporting group title | Phase 1 (LA/mGC) Cohort 2 (DL -1): T-DM1 + Cape |
| Reporting group description: | |
| In Phase 1, Cohort 2 participants (with LA/mGC) received trastuzumab emtansine at a dose of 2.4 mg/kg via IV infusion on Day 1 (Day 2 of first week) of every week along with capecitabine at a dose level of 700 mg/m ² via tablet orally twice daily on Days 1-14 followed by a 7-day rest period, in each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Reporting group title | Phase 2 (mBC): T-DM1 + Cape |
| Reporting group description: | |
| In Phase 2, participants (with mBC) who were randomized to this group received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle along with capecitabine at a dose level of 700 mg/m ² via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Reporting group title | Phase 2 (mBC): T-DM1 |
| Reporting group description: | |
| In Phase 2, participants (with mBC) who were randomized to this group received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor. | |

| Reporting group values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL -1): T-DM1 + Cape | Phase 1 (LA/mGC) Cohort 2 (DL -1): T-DM1 + Cape |
|--------------------------------------|--|---|--|
| Number of subjects | 7 | 5 | 6 |
| Age categorical Units: Subjects | | | |
| Age Continuous Units: years | | | |
| arithmetic mean | 55.9 | 50.8 | 60.0 |
| standard deviation | ± 10.75 | ± 7.76 | ± 7.40 |
| Sex: Female, Male Units: Subjects | | | |
| Female | 6 | 5 | 0 |
| Male | 1 | 0 | 6 |

| | | | |
|--|---|---|---|
| Race, Customized | | | |
| Units: Subjects | | | |
| Race: Caucasian | 6 | 4 | 6 |
| Race: N/A (as per local regulation) | 1 | 1 | 0 |
| Race: Black | 0 | 0 | 0 |
| Race: Asian | 0 | 0 | 0 |
| Race: Mixed | 0 | 0 | 0 |
| Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Ethnicity: Hispanic/Latino | 0 | 1 | 0 |
| Ethnicity: Chinese | 0 | 0 | 0 |
| Ethnicity: Other | 6 | 0 | 0 |
| Ethnicity: N/A (as per local regulation) | 1 | 1 | 6 |
| Ethnicity: Unknown | 0 | 2 | 0 |
| Ethnicity: Mixed | 0 | 1 | 0 |

| Reporting group values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | Total |
|------------------------|-----------------------------|----------------------|-------|
| Number of subjects | 81 | 80 | 179 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|---------|---------|-----|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 53.4 | 52.7 | |
| standard deviation | ± 11.71 | ± 11.33 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 80 | 80 | 171 |
| Male | 1 | 0 | 8 |
| Race, Customized | | | |
| Units: Subjects | | | |
| Race: Caucasian | 70 | 67 | 153 |
| Race: N/A (as per local regulation) | 10 | 7 | 19 |
| Race: Black | 0 | 2 | 2 |
| Race: Asian | 1 | 1 | 2 |
| Race: Mixed | 0 | 3 | 3 |
| Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Ethnicity: Hispanic/Latino | 5 | 10 | 16 |
| Ethnicity: Chinese | 1 | 0 | 1 |
| Ethnicity: Other | 38 | 36 | 80 |
| Ethnicity: N/A (as per local regulation) | 32 | 30 | 70 |
| Ethnicity: Unknown | 5 | 4 | 11 |
| Ethnicity: Mixed | 0 | 0 | 1 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape |
| Reporting group description: In Phase 1, Cohort 1 participants (with mBC) received trastuzumab emtansine (T-DM1) at a dose of 3.6 milligrams per kilogram (mg/kg) via intravenous (IV) infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine (Cape) at a dose level (DL) of 750 milligrams per meter squared (mg/m ²) via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, disease progression (PD), death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Reporting group title | Phase 1 (mBC) Cohort 1 (DL -1): T-DM1 + Cape |
| Reporting group description: In Phase 1, Cohort 1 participants (with mBC) received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine at a dose level of 700 mg/m ² via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Reporting group title | Phase 1 (LA/mGC) Cohort 2 (DL -1): T-DM1 + Cape |
| Reporting group description: In Phase 1, Cohort 2 participants (with LA/mGC) received trastuzumab emtansine at a dose of 2.4 mg/kg via IV infusion on Day 1 (Day 2 of first week) of every week along with capecitabine at a dose level of 700 mg/m ² via tablet orally twice daily on Days 1-14 followed by a 7-day rest period, in each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Reporting group title | Phase 2 (mBC): T-DM1 + Cape |
| Reporting group description: In Phase 2, participants (with mBC) who were randomized to this group received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle along with capecitabine at a dose level of 700 mg/m ² via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Reporting group title | Phase 2 (mBC): T-DM1 |
| Reporting group description: In Phase 2, participants (with mBC) who were randomized to this group received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor. | |
| Subject analysis set title | Phase 1 (mBC) Cohort 1: T-DM1 + Cape |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: In Phase 1, Cohort 1 participants (with mBC) received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine at a dose level of 700 or 750 mg/m ² via tablet orally twice daily on Days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor. | |
| Subject analysis set title | Phase 1 (mBC) Cohort 1 (DL -1): T-DM1 + Cape |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: In Phase 1, participants with mBC received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine at a dose level of 700 mg/m ² via tablet orally twice daily on days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor. | |

Primary: Phase 1 (mBC): Percentage of Participants with Dose-Limiting Toxicities (DLTs)

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|-----------------|--|
| End point title | Phase 1 (mBC): Percentage of Participants with Dose-Limiting Toxicities (DLTs) ^{[1][2]} |
|-----------------|--|

End point description:

A DLT was defined as any one of the following study treatment-related toxicities: Uncomplicated Grade 4 thrombocytopenia that does not recover before Day 21; thrombocytopenia complicated with clinically significant bleeding requiring medical intervention; Grade 4 neutropenia lasting more than (>) 7 consecutive days; febrile neutropenia with absolute neutrophil count (ANC) less than (<) 1000 cells/millimeter cube (mm³); Grade ≥3 diarrhea or Grade 3 hand-foot syndrome (in absence of dihydropyrimidine dehydrogenase [DPD] deficiency, only for DL 1); any other Grade ≥3 toxicity prohibiting start of Cycle 2; Grade 2 toxicity requiring treatment interruption for >14 days (>7 days for DL 1); for DL -1 only: <14 full doses of capecitabine; Cycle 2 dose level <100 percent (%). Analysis was performed on Phase 1 DLT-evaluable population for mBC cohort, which included all enrolled and treated mBC participants who did not experience any major protocol deviation and completed Cycle 1.

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

End point timeframe:

Continuously during Cycle 1 (up to 3 weeks)

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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

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

Justification: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 5 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 33.3 | 0.0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1 (mBC): MTD of Capecitabine when Combined with Trastuzumab Emtansine (3.6 mg/kg every 3 weeks)

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|-----------------|--|
| End point title | Phase 1 (mBC): MTD of Capecitabine when Combined with Trastuzumab Emtansine (3.6 mg/kg every 3 weeks) ^[3] |
|-----------------|--|

End point description:

MTD was defined as the dose level for which the probability of DLT is equal to a protocol-specified target probability. A DLT was defined as any one of the following study treatment related toxicities: Uncomplicated Grade 4 thrombocytopenia that does not recover before Day 21; thrombocytopenia complicated with clinically significant bleeding requiring medical intervention; Grade 4 neutropenia lasting >7 consecutive days; febrile neutropenia with ANC <1000 cells/mm³; Grade ≥3 diarrhea or Grade 3 hand-foot syndrome (in absence of DPD deficiency only for DL 1); any other Grade ≥3 toxicity prohibiting start of Cycle 2; Grade 2 toxicity requiring treatment interruption for >14 days (>7 days for DL 1); for DL -1 only: <14 full doses of capecitabine; Cycle 2 dose level <100%. Analysis was performed on Phase 1 DLT-evaluable population for mBC cohort.

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

End point timeframe:

Continuously during Cycle 1 (up to 3 weeks)

Notes:

[3] - 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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Phase 1 (mBC) Cohort 1: T-DM1 + Cape | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 11 | | | |
| Units: mg/m ² | | | | |
| number (not applicable) | 700 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2 (mBC): Percentage of Participants with Best Overall Response (BOR) as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|--|
| End point title | Phase 2 (mBC): Percentage of Participants with Best Overall Response (BOR) as Assessed by the Investigator According to RECIST v1.1 ^[4] |
|-----------------|--|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. BOR was defined as percentage of participants with a complete response (CR) or partial response (PR) that was confirmed by repeat assessments ≥ 4 weeks after initial documentation. CR was defined as the disappearance of all target lesions (TLs) and non-TLs; short axis (SA) reduction to < 10 millimeters (mm) for nodal TLs/non-TLs; and no new lesions. PR was defined as $\geq 30\%$ decrease in sum of diameters (SoD) of TLs, taking as reference the baseline SoD; no progression in non-TLs; and no new lesions. The 90% confidence Interval (CI) was computed using Clopper-Pearson approach. Analysis was performed on Intent-to-Treat (ITT) Population, which included all participants in the randomized Phase 2 part of the study.

Participants were analyzed as per the initial randomization. Participants without tumor assessment after start of study treatment were considered as non-responders.

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

End point timeframe:

Baseline until CR/PR, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| | | | | |
|-----------------------------------|-----------------------------|----------------------|--|--|
| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 90%) | 44.4 (35.0 to 54.2) | 36.3 (27.3 to 46.0) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Phase 2 (mBC): T-DM1 + Cape v Phase 2 (mBC): T-DM1 |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.336 |
| Method | Fisher exact |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 8.2 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -4.5 |
| upper limit | 20.9 |

Notes:

[5] - 90% CI was estimated using Hauck-Anderson approach.

Primary: Phase 1 (LA/mGC): Percentage of Participants with DLTs

| | |
|---|--|
| End point title | Phase 1 (LA/mGC): Percentage of Participants with DLTs ^{[6][7]} |
| End point description: | |
| A DLT was defined as any one of the following study treatment related toxicities: Uncomplicated Grade 4 thrombocytopenia that does not recover before Day 21; thrombocytopenia complicated with clinically significant bleeding requiring medical intervention; Grade 4 neutropenia lasting >7 consecutive days; febrile neutropenia with ANC <1000 cells/mm ³ ; Grade ≥3 diarrhea or Grade 3 hand-foot syndrome; any other Grade ≥3 toxicity prohibiting start of Cycle 2; Grade 2 toxicity requiring treatment interruption for >14 days; <14 full doses of capecitabine; Cycle 2 dose level <100%. Analysis was performed on Phase 1 DLT-evaluable population for LA/mGC Cohort, which included all enrolled and treated LA/mGC participants who did not experience any major protocol deviation and completed Cycle 1. | |
| End point type | Primary |
| End point timeframe: | |
| Continuously during 3 weeks | |

Notes:

[6] - 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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

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

Justification: Reported analysis was planned to be carried out in the indicated arm(s) only.

| | | | | |
|-----------------------------------|--|--|--|--|
| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0.0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1 (LA/mGC): MTD of Capecitabine when Combined with Trastuzumab Emtansine (2.4 mg/kg QW)

| | |
|-----------------|---|
| End point title | Phase 1 (LA/mGC): MTD of Capecitabine when Combined with Trastuzumab Emtansine (2.4 mg/kg QW) ^{[8][9]} |
|-----------------|---|

End point description:

MTD was defined as the dose level for which the probability of DLT is equal to a protocol-specified target probability. A DLT was defined as any one of the following study treatment related toxicities: Uncomplicated Grade 4 thrombocytopenia that does not recover before Day 21; thrombocytopenia complicated with clinically significant bleeding requiring medical intervention; Grade 4 neutropenia lasting >7 consecutive days; febrile neutropenia with ANC <1000 cells/mm³; Grade >=3 diarrhea or Grade 3 hand-foot syndrome; any other Grade >=3 toxicity prohibiting start of Cycle 2; Grade 2 toxicity requiring treatment interruption for >14 days; <14 full doses of capecitabine; Cycle 2 dose level <100%. Analysis was performed on Phase 1 DLT-evaluable population for LA/mGC cohort.

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

End point timeframe:

Continuously during 3 weeks

Notes:

[8] - 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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

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

Justification: Reported analysis was planned to be carried out in the indicated arm(s) only.

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: mg/m ² | | | | |
| number (not applicable) | 700 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): Percentage of Participants with BOR as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|---|
| End point title | Phase 1 (mBC): Percentage of Participants with BOR as Assessed by the Investigator According to RECIST v1.1 ^[10] |
|-----------------|---|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. BOR in Phase 1 was defined as percentage of participants with a CR or PR. CR was defined as the disappearance of all TLs and non-TLs; SA reduction to <10 mm for nodal TLs/non-TLs; and no new lesions. PR was defined as >=30% decrease in SoD of TLs, taking as reference the baseline SoD; no progression in non-TLs; and no new lesions. Analysis was performed on Phase 1 DLT-evaluable population for mBC cohort.

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

End point timeframe:

Baseline until CR/PR, consent withdrawal, or study end whichever occurred first (up to approximately

Notes:

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

Justification: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 5 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 83.3 | 100.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): Serum Concentration of Trastuzumab Emtansine

| | |
|-----------------|---|
| End point title | Phase 1 (mBC): Serum Concentration of Trastuzumab Emtansine ^[11] |
|-----------------|---|

End point description:

Analysis was performed on Phase 1 pharmacokinetic (PK) analysis population for mBC cohort, which included all mBC participants who received at least one dose of study medication during Phase 1 and had at least one reported serum or plasma result for PK.

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

End point timeframe:

Pre-trastuzumab emtansine dose (0 hour [h]) on Day 1 Cycle 2; 15-30 minutes (min) after end of trastuzumab emtansine infusion (maximum infusion duration = 90 min) on Day 2 Cycle 1 and Day 1 Cycle 2 (cycle length=21 days)

Notes:

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

Justification: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: micrograms per milliliter (mcg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1, Post-dose | 81.3 (± 13.3) | 78.6 (± 14.6) | | |
| Cycle 2, Pre-dose | 1.17 (± 1.25) | 2.1 (± 1.49) | | |
| Cycle 2, Post-dose | 70.5 (± 13.3) | 78.5 (± 14.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): Serum Concentration of Trastuzumab

| | |
|-----------------|---|
| End point title | Phase 1 (mBC): Serum Concentration of Trastuzumab ^[12] |
|-----------------|---|

End point description:

Trastuzumab was derived from trastuzumab emtansine. Analysis was performed on Phase 1 PK analysis population for mBC cohort.

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

End point timeframe:

Pre-trastuzumab emtansine dose (0 h) on Day 1 Cycle 2; 15-30 min after end of trastuzumab emtansine infusion (maximum infusion duration = 90 min) on Day 2 Cycle 1 and Day 1 Cycle 2 (cycle length=21 days)

Notes:

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

Justification: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1, Post-dose | 89.1 (± 24.37) | 92.9 (± 22.13) | | |
| Cycle 2, Pre-dose | 11.8 (± 13.28) | 14.0 (± 12.53) | | |
| Cycle 2, Post-dose | 74.8 (± 18.89) | 94.7 (± 24.60) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): Maximum Observed Plasma Concentration (Cmax) of Capecitabine

| | |
|-----------------|---|
| End point title | Phase 1 (mBC): Maximum Observed Plasma Concentration (Cmax) of Capecitabine ^[13] |
|-----------------|---|

End point description:

Cmax for Capecitabine was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for percent coefficient of variation (CV%). Analysis was performed on Phase 1 PK analysis population for mBC cohort.

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

End point timeframe:

Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1

Notes:

[13] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (geometric coefficient of variation) | 2990 (\pm 38.4) | 5652 (\pm 91.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): Area Under the Plasma Concentration-Time Curve From Time Zero to infinity (AUC[0-inf]) of Capecitabine

| | |
|-----------------|---|
| End point title | Phase 1 (mBC): Area Under the Plasma Concentration-Time Curve From Time Zero to infinity (AUC[0-inf]) of Capecitabine ^[14] |
|-----------------|---|

End point description:

AUC(0-inf) is the measure of total drug exposure and is dependent on the total amount of drug absorbed. AUC(0-inf) for capecitabine was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for mBC cohort.

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

End point timeframe:

Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1

Notes:

[14] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: hours*nanograms per milliliter (h*ng/mL) | | | | |
| arithmetic mean (geometric coefficient of variation) | 3973 (\pm 38.0) | 5440 (\pm 57.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): Plasma Terminal Half-Life (t_{1/2}) of Capecitabine

| | |
|-----------------|--|
| End point title | Phase 1 (mBC): Plasma Terminal Half-Life (t _{1/2}) of Capecitabine ^[15] |
|-----------------|--|

End point description:

Plasma terminal half-life is the time measured for the plasma drug concentration to decrease by one half during the elimination phase of the drug. $t_{1/2}$ for capecitabine was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for mBC cohort.

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

End point timeframe:

Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1

Notes:

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

Justification: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|--|---|---|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: hours | | | | |
| arithmetic mean (geometric coefficient of variation) | 0.70 (\pm 131.9) | 0.39 (\pm 38.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): Cmax of 5-Fluorouracil (Metabolite of Capecitabine)

| | |
|-----------------|--|
| End point title | Phase 1 (mBC): Cmax of 5-Fluorouracil (Metabolite of Capecitabine) ^[16] |
|-----------------|--|

End point description:

5-fluorouracil is a metabolite of capecitabine. Cmax for 5-fluorouracil was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for mBC cohort.

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

End point timeframe:

Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1

Notes:

[16] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|--|---|---|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: ng/mL | | | | |
| arithmetic mean (geometric coefficient of variation) | 148 (\pm 49.9) | 143 (\pm 45.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): AUC(0-inf) of 5-Fluorouracil (Metabolite of Capecitabine)

| | |
|-----------------|--|
| End point title | Phase 1 (mBC): AUC(0-inf) of 5-Fluorouracil (Metabolite of Capecitabine) ^[17] |
|-----------------|--|

End point description:

5-fluorouracil is a metabolite of capecitabine. AUC(0-inf) is the measure of total drug exposure and is dependent on the total amount of drug absorbed. AUC(0-inf) for 5-fluorouracil was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for mBC cohort.

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

End point timeframe:

Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1

Notes:

[17] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|--|---|---|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: h*ng/mL | | | | |
| arithmetic mean (geometric coefficient of variation) | 257 (± 49.9) | 244 (± 38.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (mBC): t1/2 of 5-Fluorouracil (Metabolite of Capecitabine)

| | |
|-----------------|--|
| End point title | Phase 1 (mBC): t1/2 of 5-Fluorouracil (Metabolite of Capecitabine) ^[18] |
|-----------------|--|

End point description:

5-fluorouracil is a metabolite of capecitabine. Plasma terminal half-life is the time measured for the plasma drug concentration to decrease by one half during the elimination phase of the drug. t1/2 for 5-fluorouracil was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for mBC cohort.

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

End point timeframe:

Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1

Notes:

[18] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL - 1): T-DM1 + Cape | | |
|--|---|---|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: hours | | | | |
| arithmetic mean (geometric coefficient of variation) | 0.63 (\pm 39.5) | 0.64 (\pm 18.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Time to Response (TTR) as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|--|
| End point title | Phase 2 (mBC): Time to Response (TTR) as Assessed by the Investigator According to RECIST v1.1 ^[19] |
|-----------------|--|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. TTR was defined as the time (in months) from randomization to first documentation of confirmed PR or CR (whichever occurred first). CR was defined as the disappearance of all TLs and non-TLs; SA reduction to <10 mm for nodal TLs/non-TLs; and no new lesions. PR was defined as \geq 30% decrease in SoD of TLs, taking as reference the baseline SoD; no progression in non-TLs; and no new lesions. Analysis was performed on ITT Population. Only participants with a BOR of CR or PR were included in the analysis.

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

End point timeframe:

Baseline until first documentation of confirmed PR or CR, whichever occurred first (up to approximately 2.5 years overall)

Notes:

[19] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|-------------------------------|-----------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 29 | | |
| Units: months | | | | |
| median (full range (min-max)) | 2.10 (1.2 to 10.8) | 2.10 (1.9 to 8.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Duration of Response (DoR) as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|--|
| End point title | Phase 2 (mBC): Duration of Response (DoR) as Assessed by the Investigator According to RECIST v1.1 ^[20] |
|-----------------|--|

End point description:

DoR was defined as the time (in months) from the date of first recorded PR/CR until the date of PD or death from any cause. According to RECIST v1.1, CR: the disappearance of all TLs and non-TLs, SA reduction to <10 mm for nodal TLs/non-TLs, and no new lesions; PR: $\geq 30\%$ decrease in SoD of TLs (taking as reference the baseline SoD), no progression in non-TLs, and no new lesions; PD: $\geq 20\%$ relative increase with ≥ 5 mm of absolute increase in the SoD (taking as reference the smallest SoD recorded since treatment started), 1 or more new lesions, and/or unequivocal progression of non-TLs. Participants with no documented PD after CR/PR were censored at the time of last tumor assessment. Participants without post-baseline tumor assessment were censored at randomization plus 1 day. The median DOR and 90% CI were estimated using Kaplan-Meier method. '99999'=Upper limit of 90% CI could not be calculated due to insufficient number of participants who had an event.

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

End point timeframe:

From the documentation of response until PD, death, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[20] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|----------------------------------|-----------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[21] | 29 ^[22] | | |
| Units: months | | | | |
| median (confidence interval 90%) | 11.30 (8.61 to 99999) | 12.22 (8.84 to 15.97) | | |

Notes:

[21] - ITT Population participants with a BOR of CR or PR were included in the analysis.

[22] - ITT Population participants with a BOR of CR or PR were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Percentage of Participants with PD as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|--|
| End point title | Phase 2 (mBC): Percentage of Participants with PD as Assessed by the Investigator According to RECIST v1.1 ^[23] |
|-----------------|--|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. PD was defined as $\geq 20\%$ relative increase with ≥ 5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-TLs. Analysis was performed on ITT Population.

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

End point timeframe:

Baseline until PD, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[23] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|-----------------------------------|-----------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 64.2 | 70.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Time to Progression (TTP) as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|---|
| End point title | Phase 2 (mBC): Time to Progression (TTP) as Assessed by the Investigator According to RECIST v1.1 ^[24] |
|-----------------|---|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. TTP was defined as the time (in months) from randomization to the first occurrence of PD. PD was defined as $\geq 20\%$ relative increase with ≥ 5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-TLs. Participants with no documented PD at the time of study end (including participants who died before PD) or who were lost to follow-up were censored on the date of the last tumor assessment. The median TTP and 90% CI was estimated using Kaplan-Meier method. Analysis was performed on ITT Population.

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

End point timeframe:

Baseline until PD, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[24] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|----------------------------------|-----------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: months | | | | |
| median (confidence interval 90%) | 10.38 (7.85 to 12.91) | 10.32 (7.56 to 13.27) | | |

Statistical analyses

Secondary: Phase 2 (mBC): Percentage of Participants with Treatment Failure as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|---|
| End point title | Phase 2 (mBC): Percentage of Participants with Treatment Failure as Assessed by the Investigator According to RECIST v1.1 ^[25] |
|-----------------|---|

End point description:

Treatment failure was defined as occurrence of any of the following event while on treatment: PD, death, withdrawal due to adverse event (AE) or laboratory abnormality, or refusal of treatment. PD as assessed by the investigator according to RECIST v1.1 was defined as $\geq 20\%$ relative increase with ≥ 5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-TLs. Analysis was performed on ITT Population.

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

End point timeframe:

Baseline until treatment failure, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[25] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|-----------------------------------|-----------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 77.8 | 83.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Time to Treatment Failure (TTF) as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|---|
| End point title | Phase 2 (mBC): Time to Treatment Failure (TTF) as Assessed by the Investigator According to RECIST v1.1 ^[26] |
|-----------------|---|

End point description:

TTF was defined as the time (in months) from randomization until treatment failure (PD, death, withdrawal due to AE or laboratory abnormality, or refusal of treatment). PD as assessed by the investigator according to RECIST v1.1 was defined as $\geq 20\%$ relative increase with ≥ 5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-TLs. Participants who did not experience any of the above events while on study were censored on the date of their last tumor assessment. The median TTF and 90% CI was estimated using Kaplan-Meier method. Analysis was performed on ITT Population.

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

End point timeframe:

Baseline until treatment failure, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[26] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|----------------------------------|-----------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: months | | | | |
| median (confidence interval 90%) | 9.86 (7.62 to 10.68) | 7.66 (6.54 to 10.68) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Percentage of Participants With PD as Assessed by the Investigator According to RECIST v1.1 or Death from any Cause

| | |
|-----------------|--|
| End point title | Phase 2 (mBC): Percentage of Participants With PD as Assessed by the Investigator According to RECIST v1.1 or Death from any Cause ^[27] |
|-----------------|--|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. PD was defined as $\geq 20\%$ relative increase with ≥ 5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-TLs. Analysis was performed on ITT Population.

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

End point timeframe:

Baseline until PD, death from any cause, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[27] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|-----------------------------------|-----------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 67.9 | 73.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Progression-Free Survival (PFS) as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|---|
| End point title | Phase 2 (mBC): Progression-Free Survival (PFS) as Assessed by the Investigator According to RECIST v1.1 ^[28] |
|-----------------|---|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. PFS was defined as the time (in months) from randomization until the first documented PD or death from any cause, whichever occurred first. PD was defined as $\geq 20\%$ relative increase with ≥ 5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-TLs. Participants with no PFS events were censored on the date of the last tumor assessment. Participants without post-baseline tumor assessment were censored at randomization plus 1 day. The median PFS and 90% CI was estimated using Kaplan-Meier method. Analysis was performed on ITT Population.

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

End point timeframe:

Baseline until PD, death from any cause, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[28] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|----------------------------------|-----------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: months | | | | |
| median (confidence interval 90%) | 10.15 (7.85 to 12.55) | 9.82 (7.46 to 13.08) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Percentage of Participants with Clinical Benefit as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|--|
| End point title | Phase 2 (mBC): Percentage of Participants with Clinical Benefit as Assessed by the Investigator According to RECIST v1.1 ^[29] |
|-----------------|--|

End point description:

The clinical benefit was defined as a confirmed response of CR, PR, or stable disease (SD) that lasted for at least 6 months. Tumor response was assessed by the investigator according to RECIST v1.1. CR: the disappearance of all TLs and non-TLs; SA reduction to < 10 mm for nodal TLs/non-TLs; and no new lesions. PR: $\geq 30\%$ decrease in SoD of TLs, taking as reference the baseline SoD; no progression in non-TLs; and no new lesions. PD: $\geq 20\%$ relative increase with ≥ 5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-TLs. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SoD on study. The 90% CI was computed using Clopper-Pearson approach. Analysis was performed on ITT Population.

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

End point timeframe:

Baseline until clinical benefit response, consent withdrawal, or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[29] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|-----------------------------------|-----------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 90%) | 66.7 (57.1 to 75.3) | 62.5 (52.7 to 71.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Percentage of Participants who Died of any Cause

| | |
|-----------------|---|
| End point title | Phase 2 (mBC): Percentage of Participants who Died of any Cause ^[30] |
|-----------------|---|

End point description:

Analysis was performed on ITT Population.

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

End point timeframe:

Baseline until death or study end whichever occurred first (up to approximately 2.5 years overall)

Notes:

[30] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|-----------------------------------|-----------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 22.2 | 26.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 (mBC): Overall Survival (OS)

| | |
|-----------------|--|
| End point title | Phase 2 (mBC): Overall Survival (OS) ^[31] |
|-----------------|--|

End point description:

OS was defined as the time (in months) from randomization until death from any cause. Participants who were alive at the time of data cut-off were censored on the date of the last follow-up assessment.

Participants who were lost to follow-up were censored on the date of last contact. The median OS and 90% CI was estimated using Kaplan-Meier method. Analysis was performed on ITT Population. The data '99999' in the results signifies that Median and/or 90% CI could not be calculated due to insufficient number of participants who had an event.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline until death or study end whichever occurred first (up to approximately 2.5 years overall) | |

Notes:

[31] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | | |
|----------------------------------|-----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 80 | | |
| Units: months | | | | |
| median (confidence interval 90%) | 99999 (99999 to 99999) | 24.71 (24.28 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): Percentage of Participants with BOR as Assessed by the Investigator According to RECIST v1.1

| | |
|-----------------|--|
| End point title | Phase 1 (LA/mGC): Percentage of Participants with BOR as Assessed by the Investigator According to RECIST v1.1 ^[32] |
|-----------------|--|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. BOR in Phase 1 was defined as percentage of participants with a CR or PR. CR was defined as the disappearance of all TLs and non-TLs; SA reduction to <10 mm for nodal TLs/non-TLs; and no new lesions. PR was defined as ≥30% decrease in SoD of TLs, taking as reference the baseline SoD; no progression in non-TLs; and no new lesions. Analysis was performed on Phase 1 DLT-evaluable population for LA/mGC cohort.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline until CR/PR, consent withdrawal, or study end whichever occurred first (up to approximately 1.5 years overall) | |

Notes:

[32] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 83.3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): Serum Concentration of Trastuzumab Emtansine

| | |
|-----------------|--|
| End point title | Phase 1 (LA/mGC): Serum Concentration of Trastuzumab Emtansine ^[33] |
|-----------------|--|

End point description:

Analysis was performed on Phase 1 PK analysis population for LA/mGC cohort.

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

End point timeframe:

Pre-trastuzumab emtansine dose (0 h) on Day 1 Cycle 2; 15-30 min after end of trastuzumab emtansine infusion (maximum infusion duration = 90 min) on Day 2 Cycle 1 and Day 1 Cycle 2 (cycle length=21 days)

Notes:

[33] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1, Post-dose | 30.1 (± 14.5) | | | |
| Cycle 2, Pre-dose | 10.1 (± 5.85) | | | |
| Cycle 2, Post-dose | 46.4 (± 7.74) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): Serum Concentration of Trastuzumab

| | |
|-----------------|--|
| End point title | Phase 1 (LA/mGC): Serum Concentration of Trastuzumab ^[34] |
|-----------------|--|

End point description:

Trastuzumab was derived from trastuzumab emtansine. Analysis was performed on Phase 1 PK analysis population for LA/mGC cohort.

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

End point timeframe:

Pre-trastuzumab emtansine dose (0 h) on Day 1 Cycle 2; 15-30 min after end of trastuzumab emtansine infusion (maximum infusion duration = 90 min) on Day 2 Cycle 1 and Day 1 Cycle 2 (cycle length=21

days)

Notes:

[34] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1, Post-dose | 33.1 (± 15.98) | | | |
| Cycle 2, Pre-dose | 18.5 (± 7.57) | | | |
| Cycle 2, Post-dose | 57.6 (± 13.55) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): Cmax of Capecitabine

| | |
|-----------------|--|
| End point title | Phase 1 (LA/mGC): Cmax of Capecitabine ^[35] |
|-----------------|--|

End point description:

Cmax for capecitabine was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for LA/mGC cohort.

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

End point timeframe:

Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1

Notes:

[35] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
|--|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (geometric coefficient of variation) | 4925 (± 36.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): AUC(0-inf) of Capecitabine

| | |
|---|--|
| End point title | Phase 1 (LA/mGC): AUC(0-inf) of Capecitabine ^[36] |
| End point description: AUC(0-inf) is the measure of total drug exposure and is dependent on the total amount of drug absorbed. AUC(0-inf) for capecitabine was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for LA/mGC cohort. | |
| End point type | Secondary |
| End point timeframe: Pre-capecitabine dose (0h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1 | |
| Notes: [36] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only. | |

| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
|--|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: h*ng/mL | | | | |
| arithmetic mean (geometric coefficient of variation) | 5131 (\pm 24.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): t1/2 of Capecitabine

| | |
|--|--|
| End point title | Phase 1 (LA/mGC): t1/2 of Capecitabine ^[37] |
| End point description: Plasma terminal half-life is the time measured for the plasma drug concentration to decrease by one half during the elimination phase of the drug. t1/2 for capecitabine was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for LA/mGC cohort. | |
| End point type | Secondary |
| End point timeframe: Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1 | |
| Notes: [37] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only. | |

| | | | | |
|--|---|--|--|--|
| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: hours | | | | |
| arithmetic mean (geometric coefficient of variation) | 0.65 (± 34.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): Cmax of 5-Fluorouracil (Metabolite of Capecitabine)

| | |
|-----------------|---|
| End point title | Phase 1 (LA/mGC): Cmax of 5-Fluorouracil (Metabolite of Capecitabine) ^[38] |
|-----------------|---|

End point description:

5-fluorouracil is a metabolite of capecitabine. Cmax for 5-fluorouracil was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for LA/mGC cohort.

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

End point timeframe:

Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1

Notes:

[38] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| | | | | |
|--|---|--|--|--|
| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (geometric coefficient of variation) | 137 (± 24.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): AUC(0-inf) of 5-Fluorouracil (Metabolite of Capecitabine)

| | |
|-----------------|---|
| End point title | Phase 1 (LA/mGC): AUC(0-inf) of 5-Fluorouracil (Metabolite of Capecitabine) ^[39] |
|-----------------|---|

End point description:

5-fluorouracil is a metabolite of capecitabine. AUC(0-inf) is the measure of total drug exposure and is

dependent on the total amount of drug absorbed. AUC(0-inf) for 5-fluorouracil was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for LA/mGC cohort.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1 | |

Notes:

[39] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| | | | | |
|--|--|--|--|--|
| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: h*ng/mL | | | | |
| arithmetic mean (geometric coefficient of variation) | 213 (\pm 16.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 (LA/mGC): t1/2 of 5-Fluorouracil (Metabolite of Capecitabine)

| | |
|-----------------|---|
| End point title | Phase 1 (LA/mGC): t1/2 of 5-Fluorouracil (Metabolite of Capecitabine) ^[40] |
|-----------------|---|

End point description:

5-fluorouracil is a metabolite of capecitabine. Plasma terminal half-life is the time measured for the plasma drug concentration to decrease by one half during the elimination phase of the drug. t1/2 for 5-fluorouracil was estimated from plasma concentration versus time data using non-compartmental methods of analysis. Reported dispersion values are for CV%. Analysis was performed on Phase 1 PK analysis population for LA/mGC cohort.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Pre-capecitabine dose (0 h) and 0.5, 1, 1.5, 2, 2.5, 4, and 6 h post-capecitabine dose on Day 1 Cycle 1 | |

Notes:

[40] - 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: Reported analysis was planned to be carried out in the indicated arm(s) only.

| | | | | |
|--|--|--|--|--|
| End point values | Phase 1 (LA/mGC) Cohort 2 (DL - 1): T-DM1 + Cape | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: hours | | | | |
| arithmetic mean (geometric coefficient of variation) | 0.83 (\pm 17.0) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 42 days after last dose (up to 4.5 years overall)

Adverse event reporting additional description:

Safety population: Participants who received ≥ 1 dose of study drug, analyzed as per actual treatment received. In Phase 2, of 161 participants, 1 was randomized in error (received no treatment) and was excluded from safety analysis and 1 who was randomized to T-DM1 alone Arm received Capecitabine throughout study and was counted in T-DM1+Cape Arm.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape |
|-----------------------|---|

Reporting group description:

In Phase 1, participants with mBC received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine at a dose level of 750 mg/m² via tablet orally twice daily on days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor.

| | |
|-----------------------|--|
| Reporting group title | Phase 1 (mBC) Cohort 1 (DL -1): T-DM1 + Cape |
|-----------------------|--|

Reporting group description:

In Phase 1, participants with mBC received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion (on Day 1 [on Day 2 for Cycle 1] of each 21-day cycle) along with capecitabine at a dose level of 700 mg/m² via tablet orally twice daily on days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor.

| | |
|-----------------------|---|
| Reporting group title | Phase 1 (LA/mGC) Cohort 2 (DL -1): T-DM1 + Cape |
|-----------------------|---|

Reporting group description:

In Phase 1, participants with LA/mGC received trastuzumab emtansine at a dose of 2.4 mg/kg via IV infusion on Day 1 (Day 2 of first week) QW along with capecitabine at a dose level of 700 mg/m² via tablet orally twice daily on days 1-14 followed by a 7-day rest period until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Phase 2 (mBC): T-DM1 + Cape |
|-----------------------|-----------------------------|

Reporting group description:

In Phase 2, participants with mBC received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle along with capecitabine at a dose level of 700 mg/m² via tablet orally twice daily on days 1-14 of each 21-day cycle until unacceptable toxicity, withdrawal of consent, PD, death, reasons deemed by the treating physician, or study termination by the sponsor.

| | |
|-----------------------|----------------------|
| Reporting group title | Phase 2 (mBC): T-DM1 |
|-----------------------|----------------------|

Reporting group description:

In Phase 2, participants with mBC received trastuzumab emtansine at a dose of 3.6 mg/kg via IV infusion on Day 1 of each 21-day cycle until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor.

| Serious adverse events | Phase 1 (mBC) Cohort 1 (DL 1): T- DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL -1): T- DM1 + Cape | Phase 1 (LA/mGC) Cohort 2 (DL -1): T- DM1 + Cape |
|---|--|---|--|
| Total subjects affected by serious adverse events subjects affected / exposed | 0 / 7 (0.00%) | 2 / 5 (40.00%) | 4 / 6 (66.67%) |

| | | | |
|--|---------------------------------|---------------------------------|----------------------------------|
| number of deaths (all causes) number of deaths resulting from adverse events | 4 | 3 | 3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour haemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 7 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 1 / 6 (16.67%) 0 / 1 0 / 0 |
| Surgical and medical procedures Tumour excision subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 7 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 1 / 6 (16.67%) 0 / 1 0 / 0 |
| Reproductive system and breast disorders Uterine polyp subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 7 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 6 (0.00%) 0 / 0 0 / 0 |
| Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 7 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 6 (0.00%) 0 / 0 0 / 0 |
| Pleurisy subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 7 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 6 (0.00%) 0 / 0 0 / 0 |
| Pulmonary embolism subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 7 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 6 (0.00%) 0 / 0 0 / 0 |
| Investigations Hepatic enzyme increased | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 | | | |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (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 |
| Fracture displacement | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (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 |
| Cerebral cyst | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (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 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 | | | |
| Thrombocytopenia | | | |

| | | | |
|---|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Intestinal haematoma | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Hepatocellular injury | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Renal and urinary disorders | | | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Anuria | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (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 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (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 |
| Infections and infestations | | | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |

| | | | |
|---|---------------|---------------|---------------|
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 related infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Wound sepsis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (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 | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | |
|---|-----------------------------|----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 82 (13.41%) | 10 / 78 (12.82%) | |
| number of deaths (all causes) | 18 | 21 | |
| number of deaths resulting from | | | |

| | | | |
|---|----------------|----------------|--|
| adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Tumour excision | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Injury, poisoning and procedural complications | | | |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture displacement | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral cyst | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal haematoma | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Renal colic | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anuria | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Device related infection | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound sepsis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape | Phase 1 (mBC) Cohort 1 (DL -1): T-DM1 + Cape | Phase 1 (LA/mGC) Cohort 2 (DL -1): T-DM1 + Cape |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 7 (100.00%) | 5 / 5 (100.00%) | 6 / 6 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| Skin papilloma subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Vascular disorders | | | |
| Flushing subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Bloody discharge subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Hot flush subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Thrombosis subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Deep vein thrombosis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Surgical and medical procedures | | | |
| Skin lesion excision subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Tooth extraction subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Tumour excision subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 17 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Fatigue | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 5 (20.00%) | 4 / 6 (66.67%) |
| occurrences (all) | 4 | 6 | 5 |
| Asthenia | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Chills | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 5 (40.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 2 / 5 (40.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 2 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 0 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 2 | 1 | 2 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Malaise | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Catheter site rash | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|----------------------|----------------------|---------------------|
| Mucosal dryness subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Impaired healing subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Reproductive system and breast disorders Breast mass subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Benign prostatic hyperplasia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 4 / 7 (57.14%) 12 | 3 / 5 (60.00%) 14 | 1 / 6 (16.67%) 1 |
| Cough subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 4 | 2 / 5 (40.00%) 3 | 2 / 6 (33.33%) 2 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 3 / 5 (60.00%) 5 | 1 / 6 (16.67%) 1 |
| Haemoptysis subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Nasal ulcer subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal inflammation | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Rales | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus disorder | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 5 (20.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 2 | 2 | 2 |
| Depression | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Affect lability | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Confusional state | | | |

| | | | |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 7 (57.14%) | 1 / 5 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 5 | 2 | 1 |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 7 (57.14%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 7 (57.14%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 4 | 0 | 1 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 0 | 1 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 2 | 0 | 2 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Aspartate aminotransferase | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Blood alkaline phosphatase increased | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Liver palpable | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 3 / 5 (60.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 6 | 5 | 0 |
| Procedural headache | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Eye contusion | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin abrasion | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin injury | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Periorbital haematoma | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Thermal burn subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Congenital, familial and genetic disorders Gilbert's syndrome subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 4 / 7 (57.14%) 12 | 3 / 5 (60.00%) 8 | 0 / 6 (0.00%) 0 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 6 | 2 / 5 (40.00%) 6 | 0 / 6 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 3 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Migraine subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 4 | 0 / 6 (0.00%) 0 |
| Balance disorder subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Hypoaesthesia | | | |

| | | | |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Amnesia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Aphonia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neurotoxicity | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Syncope | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Peripheral sensory neuropathy | | | |

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|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Restless legs syndrome subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 3 / 7 (42.86%) 6 | 4 / 5 (80.00%) 6 | 0 / 6 (0.00%) 0 |
| Neutropenia subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 3 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Anaemia subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | 1 / 5 (20.00%) 1 | 4 / 6 (66.67%) 6 |
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 2 | 1 / 5 (20.00%) 2 | 0 / 6 (0.00%) 0 |
| Deafness unilateral subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Middle ear effusion subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 2 / 6 (33.33%) 3 |
| Eye disorders | | | |
| Dry eye subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 5 (20.00%) 2 | 0 / 6 (0.00%) 0 |
| Lacrimation increased | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 5 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 1 | 3 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Eye haemorrhage | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blepharospasm | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blindness | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Keratitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pterygium | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Retinal ischaemia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | 4 / 5 (80.00%) | 3 / 6 (50.00%) |
| occurrences (all) | 15 | 10 | 5 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 3 / 5 (60.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 9 | 4 | 1 |
| Constipation | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | 4 / 5 (80.00%) | 4 / 6 (66.67%) |
| occurrences (all) | 3 | 6 | 4 |
| Gingival bleeding | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 3 / 5 (60.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 6 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 5 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 6 | 1 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 3 / 5 (60.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 4 | 1 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 5 (40.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 5 | 1 |
| Toothache | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 2 | 0 | 2 |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|----------------------------------|----------------|----------------|---------------|
| Anal haemorrhage | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chapped lips | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dental caries | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eruption | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Frequent bowel movements | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Hypoaesthesia oral subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Ascites subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Melaena subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 2 / 6 (33.33%) 2 |
| Stomatitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 2 / 6 (33.33%) 2 |
| Gastric haemorrhage subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Gastritis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 2 | 2 / 5 (40.00%) 8 | 0 / 6 (0.00%) 0 |
| Hepatocellular injury subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 2 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Jaundice subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Skin and subcutaneous tissue disorders Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 3 / 7 (42.86%) 5 | 2 / 5 (40.00%) 3 | 1 / 6 (16.67%) 1 |
| Rash macular subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 3 | 3 / 5 (60.00%) 4 | 1 / 6 (16.67%) 1 |
| Dry skin | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 5 (40.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 3 | 1 |
| Rash | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 5 (40.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Macule | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Acne | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blister | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ingrowing nail | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Onycholysis | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin mass | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Swelling face | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Onychoclasia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Erythema | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Spider naevus | | | |

| | | | |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Telangiectasia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Endocrine disorders Cushingoid subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 3 / 7 (42.86%) 12 | 1 / 5 (20.00%) 3 | 2 / 6 (33.33%) 2 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 6 | 2 / 5 (40.00%) 4 | 1 / 6 (16.67%) 1 |
| Muscle spasms subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 5 | 2 / 5 (40.00%) 5 | 1 / 6 (16.67%) 2 |
| Muscular weakness subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 2 | 2 / 5 (40.00%) 3 | 0 / 6 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 3 / 7 (42.86%) 3 | 1 / 5 (20.00%) 2 | 0 / 6 (0.00%) 0 |
| Myalgia subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 2 / 5 (40.00%) 3 | 1 / 6 (16.67%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 4 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Bone pain | | | |

| | | | |
|---------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 2 | 2 |
| Joint stiffness | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Muscle twitching | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Arthritis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Coccydynia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Limb mass | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight bearing difficulty | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 2 / 5 (40.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 5 (40.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 1 | 3 | 2 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 1 | 3 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Sinusitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Furuncle | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| Skin infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 10 | 3 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 2 / 5 (40.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 5 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 2 | 0 | 3 |
| Cell death | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 5 (20.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperglycaemia | | | |

| | | | |
|-----------------------------|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Phase 2 (mBC): T-DM1 + Cape | Phase 2 (mBC): T-DM1 | |
|---|-----------------------------|----------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 75 / 82 (91.46%) | 64 / 78 (82.05%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Bloody discharge | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Surgical and medical procedures | | | |
| Skin lesion excision | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|--|------------------------|------------------------|--|
| Tumour excision subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Fatigue subjects affected / exposed occurrences (all) | 10 / 82 (12.20%) 13 | 11 / 78 (14.10%) 18 | |
| Asthenia subjects affected / exposed occurrences (all) | 17 / 82 (20.73%) 37 | 15 / 78 (19.23%) 77 | |
| Chills subjects affected / exposed occurrences (all) | 1 / 82 (1.22%) 1 | 5 / 78 (6.41%) 5 | |
| Gait disturbance subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Pain subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 13 / 82 (15.85%) 28 | 15 / 78 (19.23%) 34 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 3 / 82 (3.66%) 5 | 4 / 78 (5.13%) 6 | |
| Influenza like illness | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Malaise subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Catheter site rash subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Mucosal dryness subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Impaired healing subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Reproductive system and breast disorders Breast mass subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Benign prostatic hyperplasia subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 15 / 82 (18.29%) 22 | 10 / 78 (12.82%) 18 | |
| Cough subjects affected / exposed occurrences (all) | 5 / 82 (6.10%) 5 | 6 / 78 (7.69%) 7 | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Haemoptysis | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nasal ulcer | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 4 / 78 (5.13%) | |
| occurrences (all) | 3 | 5 | |
| Nasal inflammation | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rales | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sinus disorder | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|---------------------------------------|------------------|------------------|--|
| Depression | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Affect liability | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 27 / 82 (32.93%) | 31 / 78 (39.74%) | |
| occurrences (all) | 49 | 63 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 12 / 82 (14.63%) | 13 / 78 (16.67%) | |
| occurrences (all) | 23 | 33 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 20 / 82 (24.39%) | 24 / 78 (30.77%) | |
| occurrences (all) | 31 | 48 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 6 / 82 (7.32%) | 4 / 78 (5.13%) | |
| occurrences (all) | 23 | 8 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 9 / 82 (10.98%) | 10 / 78 (12.82%) | |
| occurrences (all) | 11 | 14 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 8 / 82 (9.76%) | 16 / 78 (20.51%) | |
| occurrences (all) | 15 | 24 | |
| Aspartate aminotransferase | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Weight decreased | | | |

| | | | |
|--|----------------|------------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 15 / 78 (19.23%) | |
| occurrences (all) | 5 | 24 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Liver palpable | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Procedural headache | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eye contusion | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin abrasion | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Skin injury subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Periorbital haematoma subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Thermal burn subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Congenital, familial and genetic disorders Gilbert's syndrome subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 82 (1.22%) 1 | 5 / 78 (6.41%) 5 | |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 8 / 82 (9.76%) 8 | 5 / 78 (6.41%) 8 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 82 (2.44%) 4 | 4 / 78 (5.13%) 8 | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Migraine | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Aphonia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neurotoxicity | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 2 / 78 (2.56%) | |
| occurrences (all) | 5 | 3 | |
| Dysgeusia | | | |

| | | | |
|--------------------------------------|------------------|------------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 35 / 82 (42.68%) | 21 / 78 (26.92%) | |
| occurrences (all) | 93 | 35 | |
| Neutropenia | | | |
| subjects affected / exposed | 13 / 82 (15.85%) | 6 / 78 (7.69%) | |
| occurrences (all) | 19 | 6 | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 82 (10.98%) | 13 / 78 (16.67%) | |
| occurrences (all) | 12 | 15 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Middle ear effusion | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vertigo | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 6 / 82 (7.32%) | 3 / 78 (3.85%) | |
| occurrences (all) | 9 | 3 | |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eye pain | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blepharospasm | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blindness | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Keratitis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pterygium | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Retinal ischaemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|--|------------------------|------------------------|--|
| Visual impairment subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 27 / 82 (32.93%) 44 | 18 / 78 (23.08%) 55 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 82 (8.54%) 12 | 7 / 78 (8.97%) 10 | |
| Constipation subjects affected / exposed occurrences (all) | 8 / 82 (9.76%) 9 | 8 / 78 (10.26%) 18 | |
| Gingival bleeding subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Vomiting subjects affected / exposed occurrences (all) | 16 / 82 (19.51%) 17 | 8 / 78 (10.26%) 9 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 6 / 82 (7.32%) 11 | 5 / 78 (6.41%) 5 | |
| Dry mouth subjects affected / exposed occurrences (all) | 3 / 82 (3.66%) 4 | 6 / 78 (7.69%) 8 | |
| Toothache subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Abdominal distension subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 78 (0.00%) 0 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 7 / 82 (8.54%) 7 | 2 / 78 (2.56%) 2 | |
| Haematochezia | | | |

| | | | |
|----------------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Chapped lips | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eructation | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Frequent bowel movements | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gingival pain | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 5 / 78 (6.41%) | |
| occurrences (all) | 4 | 6 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 4 / 78 (5.13%) | |
| occurrences (all) | 0 | 4 | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|--|------------------|----------------|--|
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 17 / 82 (20.73%) | 2 / 78 (2.56%) | |
| occurrences (all) | 18 | 2 | |
| Rash macular | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Macule | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Acne | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 5 / 78 (6.41%) | |
| occurrences (all) | 1 | 5 | |
| Blister | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eczema | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin mass | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Swelling face | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Onychoclasia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Erythema | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash papular | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Spider naevus | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Telangiectasia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Endocrine disorders | | | |
| Cushingoid | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 11 / 82 (13.41%) | 9 / 78 (11.54%) | |
| occurrences (all) | 14 | 9 | |
| Back pain | | | |
| subjects affected / exposed | 4 / 82 (4.88%) | 4 / 78 (5.13%) | |
| occurrences (all) | 4 | 4 | |
| Muscle spasms | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 0 / 78 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal pain | | | |

| | | |
|---------------------------------|----------------|----------------|
| subjects affected / exposed | 4 / 82 (4.88%) | 6 / 78 (7.69%) |
| occurrences (all) | 5 | 8 |
| Myalgia | | |
| subjects affected / exposed | 7 / 82 (8.54%) | 2 / 78 (2.56%) |
| occurrences (all) | 8 | 3 |
| Pain in extremity | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 5 / 78 (6.41%) |
| occurrences (all) | 3 | 5 |
| Bone pain | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Joint stiffness | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Joint swelling | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Musculoskeletal chest pain | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Neck pain | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Joint range of motion decreased | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Muscle twitching | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Musculoskeletal stiffness | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Arthritis | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Coccydynia | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Limb mass | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Weight bearing difficulty | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 4 / 78 (5.13%) | |
| occurrences (all) | 1 | 4 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | |
|-----------------------------|----------------|----------------|
| Herpes zoster | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Pharyngitis | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Pneumonia | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Sinusitis | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Ear infection | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Eye infection | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Folliculitis | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Fungal skin infection | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Furuncle | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Laryngitis | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Localised infection | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |
| Oral candidiasis | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 0 |

| | | | |
|------------------------------------|------------------|------------------|--|
| Paronychia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 1 / 78 (1.28%) | |
| occurrences (all) | 5 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 82 (4.88%) | 4 / 78 (5.13%) | |
| occurrences (all) | 4 | 10 | |
| Decreased appetite | | | |
| subjects affected / exposed | 10 / 82 (12.20%) | 11 / 78 (14.10%) | |
| occurrences (all) | 21 | 41 | |
| Cell death | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperkalaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 78 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 5 / 78 (6.41%) | |
| occurrences (all) | 7 | 8 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 03 September 2013 | Dose modification guidance and DLT definition were updated in line with the most recent investigator brochure (IB) (Version 7.0); Participant retention on combination regimen was clarified to allow an additional safety follow-up and collection of tumor response data from these participants; Design of the Phase 2 part of the study was changed to the open-label, randomized exploration of efficacy and safety of the combination of trastuzumab emtansine with capecitabine compared with trastuzumab emtansine alone. Number of participants to be enrolled into Phase 2 was changed accordingly; The IDMC for Phase 2 was introduced to monitor safety outcomes. |
| 30 June 2014 | Design of the study was changed to increase the sample size for the randomized Phase 2 part from 117 participants to 210 participants; The protocol was simplified following the determination of the MTD in Phase 1 to remove information relating to dose de-escalation that was no longer relevant; The advice on contraception was updated in line with the latest trastuzumab (Herceptin) IB (Version 14). |
| 23 March 2016 | The section of risks associated with capecitabine was updated following the inclusion of the contraindication in the capecitabine summary of product characteristics (SmPC) for participants with known complete absence of DPD activity; Side effects associated with capecitabine were updated; Information regarding the risk of taking leucovorin was added as it may increase the toxicity of capecitabine; The safety reporting requirements for pregnancies was updated; Sections on assessment of causality of new AEs, AEs occurring secondary to other events, deaths, and pre-existing medical conditions were updated in line with the latest sponsor guidance; Sections describing the reporting of abnormal vital sign values, abnormal liver function tests (LFTs), and AEs associated with an overdose or error in drug administration were added; Medical monitor and statistician for the study were replaced; The number of participants in the Phase 2 part of the study were reduced from 210 participants to 160 participants, due to slow recruitment and difficulty finding participants. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The sponsor decided to terminate the study after 70% of participants had experienced a PFS event. Participants were allowed to continue treatment by enrolling into study NCT00781612 or by moving to commercial drug, depending on their country.

Notes: