

**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
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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
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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
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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
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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
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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
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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)

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

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

Analysis was performed on ITT Population.

End point type	Secondary
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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]
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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]
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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 $\geq 30\%$ decrease in SoD of TLs, taking as reference the baseline SoD; no progression in non-TLs; and no new lesions. Analysis was performed on 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]
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End point description:

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

End point type	Secondary
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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]
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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
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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]
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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
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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 (\pm 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]
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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
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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 (\pm 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]
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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 (± 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]
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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 (± 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Phase 1 (mBC) Cohort 1 (DL 1): T-DM1 + Cape
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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
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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
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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
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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
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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	0 / 7 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	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			

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 erythrodysaesthesia 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: