

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

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

Results information

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

Trial information**Trial identification**

Sponsor protocol code	BP22572
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 October 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

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

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	88
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

Participants received docetaxel (Doc) 75 milligram per square meter (mg/m²) administered intravenously on Day 1 and T-DM1 2.4 milligrams per kilogram (mg/kg) administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 75 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Dosage and administration details:

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

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

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

Participants received docetaxel 60 mg/m² administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Dosage and administration details:

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

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

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

Participants received docetaxel 60 mg/m² administered intravenously and T-DM1 2.4 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Dosage and administration details:

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

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

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

Participants received docetaxel 60 mg/m² administered intravenously and T-DM1 3.6 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 3.6 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Dosage and administration details:

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

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

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

Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 60/75/100 mg/m² administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

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

Dosage and administration details:

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

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

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

Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 60/75 mg/m² administered intravenously, and pertuzumab 840 mg (for Cycle 1) or 420 mg (for remaining cycles) on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

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

Dosage and administration details:

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

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	

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

Dosage and administration details:

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

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

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

Baseline characteristics

Reporting groups

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

Participants received docetaxel (Doc) 75 milligram per square meter (mg/m²) administered intravenously on Day 1 and T-DM1 2.4 milligrams per kilogram (mg/kg) administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 75 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Participants received docetaxel 60 mg/m² administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Participants received docetaxel 60 mg/m² administered intravenously and T-DM1 2.4 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Participants received docetaxel 60 mg/m² administered intravenously and T-DM1 3.6 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 3.6 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 60/75/100 mg/m² administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

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

Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 60/75 mg/m² administered intravenously, and pertuzumab 840 mg (for Cycle 1) or 420 mg (for remaining cycles) on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

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

Gender categorical Units: Subjects			
Female	6	6	3
Male	0	0	0

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

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

Reporting group values	Total		
Number of subjects	98		
Age categorical Units: Subjects			

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

End points

End points reporting groups

Reporting group title	MBC: T-DM1 2.4 mg/kg + Doc 75 mg/m ² (over 2 days)
Reporting group description: Participants received docetaxel (Doc) 75 milligram per square meter (mg/m ²) administered intravenously on Day 1 and T-DM1 2.4 milligrams per kilogram (mg/kg) administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 75 mg/m ² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.	
Reporting group title	MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m ² (over 2 days)
Reporting group description: Participants received docetaxel 60 mg/m ² administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m ² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.	
Reporting group title	MBC: T-DM1 2.4 mg/kg + Doc 60 mg/m ² (same day)
Reporting group description: Participants received docetaxel 60 mg/m ² administered intravenously and T-DM1 2.4 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m ² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.	
Reporting group title	MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m ² (same day)
Reporting group description: Participants received docetaxel 60 mg/m ² administered intravenously and T-DM1 3.6 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m ² was stopped and T-DM1 3.6 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.	
Reporting group title	LABC: T-DM1 + Doc (Doublet Regimen)
Reporting group description: Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 60/75/100 mg/m ² administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.	
Reporting group title	LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen)
Reporting group description: Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 60/75 mg/m ² administered intravenously, and pertuzumab 840 mg (for Cycle 1) or 420 mg (for remaining cycles) on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.	
Subject analysis set title	LABC: T-DM1 3.6 mg/kg + Doc 100 mg/m ²
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 100 mg/m ² administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.	
Subject analysis set title	LABC: T-DM1 3.6 mg/kg + Doc 75 mg/m ² + Pertuzumab 420 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 75 mg/m ² administered intravenously, and pertuzumab 420 mg on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.	
Subject analysis set title	Overall MBC Participants
Subject analysis set type	Full analysis

Subject analysis set description:

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

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

Subject analysis set description:

This analysis set included all participants enrolled in the study.

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

This analysis set included all MBC participants who received docetaxel 75 mg/m² administered intravenously.

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

Subject analysis set description:

This analysis set included all MBC participants who received docetaxel 60 mg/m² administered intravenously.

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

Subject analysis set description:

This analysis set included all LABC participants who received docetaxel 60 mg/m² administered intravenously.

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

Subject analysis set description:

This analysis set included all LABC participants who received docetaxel 75 mg/m² administered intravenously.

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

Subject analysis set description:

This analysis set included all LABC participants who received docetaxel 100 mg/m² administered intravenously.

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

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

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

that at any dose results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, results in development of drug dependency or drug abuse, is an important medical event.

Analysis population (AP): All participants who received at least one dose of study medication.

End point type	Primary
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End point timeframe:

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The study was of an explorative nature; therefore only descriptive and exploratory statistical methods were applied, and no statistical hypothesis testing was carried out.

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants with Dose Limiting Toxicity (DLT) - MBC and LABC Feasibility Population ^{[2][3]}
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End point description:

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

Febrile neutropenia; Grade greater than or equal to (\geq) 3 neurotoxicity in the form of peripheral neuropathy or peripheral neurotoxicity not improving to baseline or Grade less than or equal to (\leq) 1 at Day 21; Any non-hematological toxicity of Grade \geq 3 except for alopecia, fever, and chills, not improving to baseline or Grade \leq 1 at Day 21, despite adequate toxicity management; Any subjective intolerable toxicity felt by the investigator to be related to either study treatment; Any other treatment-related toxicity prohibiting the start of the Cycle 2 on Day 22; Fulminant skin rash.

AP: All participants who received at least one dose of study medication.

End point type	Primary
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End point timeframe:

Up to 21 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The study was of an explorative nature; therefore only descriptive and exploratory statistical methods were applied, and no statistical hypothesis testing was carried out.

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

Justification: Dose limiting toxicities were reported only in the MBC and LABC feasibility part of the study.

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
End point timeframe:	
Baseline until disease progression or death (up to 33.5 months)	

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

Statistical analyses

No statistical analyses for this end point

Secondary: PFS – MBC Population

End point title	PFS – MBC Population
End point description:	
<p>PFS was defined as the time interval between the date of the start of treatment and the date of first documentation of PD or death from any cause, whichever occurred first. Response was based on RECIST V 1.0. For TLs, PD was at least a 20 % increase in the sum of LD of TLs, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more lesions. For NTLs, PD was the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Data for participants without PD or death was censored at the time of the last response assessment. AP: All participants who received at least one dose of study medication. A total of 9 participants were censored for PFS analysis.</p>	
End point type	Secondary
End point timeframe:	
Baseline until disease progression or death (up to 33.5 months)	

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

Statistical analyses

No statistical analyses for this end point

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

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

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

AP: All participants who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline until PD or recurrence (up to 33.5 months)

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Treatment Failure - MBC Population

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

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

AP: All participants who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline until end of treatment (up to 39.8 months)

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

Statistical analyses

No statistical analyses for this end point

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

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

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

End point type	Secondary
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End point timeframe:

Baseline until end of treatment (up to 39.8 months)

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
End point timeframe:	
Baseline until PD, recurrence or death (up to 33.5 months)	

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

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response – MBC Population

End point title	Duration of Response – MBC Population
End point description:	
<p>Duration of response was calculated for participants whose best overall response was CR or PR based on the RECIST V 1.0 criteria. Duration of response was defined as the time interval between the date the CR or PR was first recorded and the date on which PD was first noted or date of death, whichever occurred first. Participants with no documented PD after CR or PR were censored at the last date at which they were known to have had the CR or PR, respectively. Median duration of response was estimated using the Kaplan-Meier method.</p> <p>AP: All participants who received at least one dose of study medication. A total of 7 participants were censored for analysis.</p>	
End point type	Secondary
End point timeframe:	
Baseline until PD, recurrence or death (up to 32.7 months)	

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants with Pathological CR (pCR) – LABC Population ^[4]
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End point description:

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

End point type	Secondary
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End point timeframe:

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

Notes:

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

Justification: pCR was reported only in the LABC part of the study.

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants with a BOR of CR or PR – LABC Population ^[5]
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End point description:

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

AP: All participants who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

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

Notes:

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

Justification: BOR of CR or PR was reported only in the LABC part of the study.

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With Anti-Therapeutic Antibody Response at Baseline and Post-Trazustumab Emtansine Dosing - MBC and LABC Population
End point description:	Percentage of participants with Human Anti-human Antibody response was reported. AP: All participants who received at least one dose of study medication.
End point type	Secondary
End point timeframe:	Baseline and post-dose (up to approximately 3 years)

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

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (C_{max}) of Serum Trastuzumab Emtansine – MBC and LABC Population

End point title	Maximum Observed Concentration (C _{max}) of Serum Trastuzumab Emtansine – MBC and LABC Population
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End point description:

Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Terminal Half-Life (t_{1/2}) of Serum Trastuzumab Emtansine – MBC and LABC Population

End point title	Apparent Terminal Half-Life (t _{1/2}) of Serum Trastuzumab Emtansine – MBC and LABC Population
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End point description:

t_{1/2} was calculated as per 'natural logarithm of 2 [ln(2)]/λ_z' formula, and λ_z was the terminal rate constant. λ_z reflects the speed of drug elimination in vivo (within the living), and was obtained from linear regression of the log-transformed terminal part of the concentration-time curve.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who

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

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	AUCinf of Serum Trastuzumab Emtansine – MBC and LABC Population
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End point description:

AUCinf is defined as the area under the serum concentration-time curve (AUC) from time 0 extrapolated to infinity.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Clearance (CL) of Serum Trastuzumab Emtansine – MBC and LABC Population
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End point description:

CL was estimated as dose divided by AUCinf.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Vss is defined as the volume of distribution at steady state.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

End point type | Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	T1/2 of Total Serum Trastuzumab – MBC and LABC Population
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End point description:

t1/2 was calculated as per 'natural logarithm of 2 [ln(2)]/λz' formula, and λz was the terminal rate constant. λz reflects the speed of drug elimination in vivo (within the living), and was obtained from linear regression of the log-transformed terminal part of the concentration-time curve.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	AUCinf of Total Serum Trastuzumab – MBC and LABC Population
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End point description:

AUCinf is defined as the AUC from time 0 extrapolated to infinity.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	CL of Total Serum Trastuzumab – MBC and LABC Population
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End point description:

CL was estimated as dose divided by AUCinf.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Vss of Total Serum Trastuzumab – MBC and LABC Population
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End point description:

Vss is defined as the volume of distribution at steady state.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Plasma DM1 – MBC and LABC Population

End point title	Cmax of Plasma DM1 – MBC and LABC Population
End point description:	
Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.	
PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.	
End point type	Secondary
End point timeframe:	
Cycle 1 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 2, Day 3, and Day 8); Cycle 2 (pre-dose, 15 minutes and 4 hours after end of infusion of T-DM1 on Day 1 and Day 8)	

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

t1/2 was calculated as per 'natural logarithm of 2 [ln(2)]/λz' formula, and λz was the terminal rate constant. λz reflects the speed of drug elimination invivo (within the living), and was obtained from linear regression of the log-transformed terminal part of the concentration-time curve.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

'99999' signifies that SD was not calculable due to only 1 participant available for PK analysis.

End point type | Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: AUCinf of Plasma DM1 – MBC and LABC Population

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

End point description:

AUCinf is the area under the serum concentration-time curve from time 0 extrapolated to infinity. Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

PK analysis population: Pharmacokinetic-evaluable participants were defined as participants who received at least one dose of T-DM1 with at least one post-dose concentration data point.

'99999' signifies that SD was not calculable due to only 1 participant available for PK analysis.

End point type | Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Docetaxel – MBC and LABC Population

End point title	Cmax of Docetaxel – MBC and LABC Population
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End point description:

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

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

End point type	Secondary
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End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	T1/2 of Docetaxel – MBC and LABC Population
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End point description:

t1/2 was calculated as per 'natural logarithm of 2 [ln(2)]/λz' formula, and λz was the terminal rate constant. λz reflects the speed of drug elimination in vivo (within the living), and was obtained from linear regression of the log-transformed terminal part of the concentration-time curve.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

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

End point type	Secondary
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End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: AUCinf of Docetaxel – MBC and LABC Population

End point title	AUCinf of Docetaxel – MBC and LABC Population
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End point description:

AUCinf is the AUC from time 0 extrapolated to infinity.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

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

End point type	Secondary
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End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: CL of Docetaxel – MBC and LABC Population

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

End point description:

CL was estimated as dose divided by AUCinf.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

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

End point type | Secondary

End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Vss of Docetaxel – MBC and LABC Population

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

End point description:

Vss is defined as the volume of distribution at steady state.

Here, Number of participants analyzed = participants evaluable for this outcome and n= participants evaluable for specified cycle.

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

End point type	Secondary
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End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

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

Participants received docetaxel 75 mg/m² administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 75 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Participants received docetaxel 60 mg/m² administered intravenously on Day 1 and T-DM1 2.4 mg/kg administered intravenously on Day 2 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent

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

Participants received docetaxel 60 mg/m² administered intravenously and T-DM1 2.4 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 2.4 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity, or withdrawal of participant consent.

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

Participants received docetaxel 60 mg/m² administered intravenously and T-DM1 3.6 mg/kg administered intravenously on Day 1 of each 3-week cycle for a minimum of 6 cycles. After 6 cycles, docetaxel 60 mg/m² was stopped and T-DM1 3.6 mg/kg was continued until confirmed evidence of disease progression, unacceptable toxicity or withdrawal of participant consent.

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

Participants received T-DM1 3.6 mg/kg administered intravenously and docetaxel 60/75/100 mg/m² administered intravenously on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

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

Participants received T-DM1 3.6 mg/kg administered intravenously, docetaxel 60/75 mg/m² administered intravenously, and pertuzumab 840 mg (for Cycle 1) or 420 mg (for remaining cycles) on Day 1 of each 3-week cycle, for 6 cycles. Study treatment was administered for up to 6 cycles or until unacceptable toxicity, and prior to surgery.

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

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

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

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

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

Serious adverse events	MBC: T-DM1 3.6 mg/kg + Doc 60 mg/m ² (same day)	LABC: T-DM1 + Doc (Doublet Regimen)	LABC: T-DM1 + Doc + Pertuzumab (Triplet Regimen)
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Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	9 / 40 (22.50%)	9 / 33 (27.27%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events			
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 40 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 40 (0.00%)	2 / 33 (6.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis in device			
subjects affected / exposed	0 / 10 (0.00%)	0 / 40 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device deployment issue			
subjects affected / exposed	1 / 10 (10.00%)	0 / 40 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 40 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 40 (2.50%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2009	Version B: <ul style="list-style-type: none">• Updated blood volume and schedule for PK sampling• Clarified that palliative radiotherapy was allowed for brain metastasis prior to study entry.
26 August 2009	Version C: Provision of better assessment of early safety parameters, via more intensive hematology and biochemistry assessments in Weeks 1 and 2 of Cycles 1-3.
02 February 2010	Version D: <ul style="list-style-type: none">• Reduction of the maximum dose docetaxel from 100 mg/m² to 75 mg/m² in first-line participants• Addition of a third Cohort of 3 to 6 participants to receive 2.4 mg/kg T-DM1 + 60 mg/m² docetaxel, administered both on Day 1 of each cycle• Addition of Dose Level 4 (T-DM1 3.6 mg/kg and docetaxel 60 mg/m² every 3 weeks) and Dose Level 5 (T-DM1 3.0 mg/kg and docetaxel 60 mg/m² every 3 weeks) to study design• Updated participants numbers and PK sampling accordingly• Clarification of the DLT criteria regarding "nonhaematological" toxicities and dose modifications for hepatotoxicity/hematologic toxicity• Addition of exclusion criterion regarding alkaline phosphatase.
16 June 2010	Version E: Permission for participants who had newly developed isolated brain metastases that were treatable with radiation to continue with study treatment until systemic progression.
18 February 2011	Version F: <ul style="list-style-type: none">• Inclusion of participants with newly diagnosed HER2-positive LABC, with option for docetaxel dose escalation• Closure of the feasibility part of the study in MBC• Removal of overall survival and time to tumour progression as secondary endpoints• Removal of censoring for non-protocol therapy from the analysis of PFS• Update of safety guidance with respect to drug-induced liver injury and pregnancy.
31 August 2011	Version G: Inclusion of addition of pertuzumab to T-DM1 and docetaxel in LABC participants.
11 October 2011	Version H: Addition of United States sites to the study.
23 February 2012	Version I: <ul style="list-style-type: none">• Increase in participant numbers in extension part for LABC• Revision of hepatotoxicity information.

13 February 2013

Version J:
Updated safety information for identified risks and adverse events of interest.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported.

Notes: