Clinical trial results:
A randomized, double-blind, parallel group, Phase III trial to compare the efficacy, safety, and immunogenicity of TX05 with Herceptin in subjects with HER2 positive early breast cancer

Summary

EudraCT number	2017-004190-13
Trial protocol	BG HU
Global end of trial date	27 November 2020

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	TX05-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03556358
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Tanvex Biologics Corp.
Sponsor organisation address	2030 Main Street, Suite 1050, Irvine, United States, CA 96214
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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	04 February 2021
Is this the analysis of the primary	Yes

completion data?	
Primary completion date	27 November 2020
Global end of trial reached?	Yes
Global end of trial date	27 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the therapeutic equivalence of TX05 (proposed biosimilar trastuzumab) to Herceptin (trastuzumab) based on the pathologic complete response (pCR) rate following neoadjuvant chemotherapy, defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ypT0/Tis ypN0), in subjects with human epidermal growth factor receptor positive (HER2+) invasive early breast cancer (EBC).

Protection of trial subjects:

This study was conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with Food and Drug Administration regulations (Code of Federal Regulations, Sections 312.50 and 312.56) and with International Council for Harmonization guidelines on Good Clinical Practice (CPMP 135/95) and with applicable regulatory requirements.

Protection of subject personal data was ensured by not including subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws. The nature and purpose of the study were fully explained to each subject (or their legally responsible guardian). The informed consent form (ICF) was explained to the subjects prior to any study procedures being performed. Each subject signed an ICF containing appropriate study and study drug information and was provided a copy of the ICF.

Appropriate study restrictions, based on the risks and discomforts anticipated to be associated with TX05 in subjects with breast cancer, were implemented including screening procedures and exclusion criteria to ensure the safety of subjects.

Background therapy:

This was a randomised, double-blinded, parallel group, equivalence, multicenter Phase III study. The study contained 8 cycles of neoadjuvant treatment and the subjects were randomized into two groups, TX05 group and Herceptin group.

For Cycles 1 to 4, the subjects in both the groups received intravenous (IV) epirubicin (75 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks. During Cycles 5 to 8, the subjects in the TX05 received IV TX05 (8 mg/kg loading dose then 6 mg/kg) and paclitaxel (175 mg/m^2) every 3 weeks, and the subjects in the Herceptin group were to receive IV Herceptin (8 mg/kg loading dose then 6 mg/kg) and paclitaxel (175 mg/m^2) every 3 weeks.

Evidence for comparator:

Herceptin was approved for marketing in the US in 1998 and in the EU in 2000.It is indicated for the treatment of HER2-overexpressing breast cancer.

Actual start date of recruitment	28 June 2018
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	Hungary: 8
Country: Number of subjects enrolled	Belarus: 38
Country: Number of subjects enrolled	Chile: 17

Country: Number of subjects enrolled	Georgia: 34
Country: Number of subjects enrolled	India: 93
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Peru: 87
Country: Number of subjects enrolled	Philippines: 37
Country: Number of subjects enrolled	Russian Federation: 327
Country: Number of subjects enrolled	Ukraine: 136
Worldwide total number of subjects	809
EEA total number of subjects	8

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)	671
From 65 to 84 years	137
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Eligibility criteria -
Signed written informed consent.
Females ≥ 18 years of age.
Planned surgical resection of breast tumor (lumpectomy or mastectomy, and SN biopsy or ALND).
Planned neoadjuvant chemotherapy.
Histologically confirmed HER2 overexpressing invasive primary operable Stage II/IIIa breast cancer.

Pre-assignment

Screening details:

CT scan of chest or MRI of chest (only if CT scan could not be performed) and bilateral mammography or ultrasound of the breast were required at Screening for all subjects. Subjects of childbearing potential were to have a blood serum pregnancy test at Screening. Physical examinations were conducted at Screening.

Pre-assignment period milestones

Number of subjects started	809
Number of subjects completed	806

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3

Period 1

Period 1 title	Treatment Period 1, Cycle 1 to Cycle 4
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	TX05

Arm description:

Epirubicin 75 mg/m2 intravenous bolus infusion and cyclophosphamide 600 mg/m2 by 30-minute IV infusion, on Day 1 of Cycle 1 and thereafter 3 weeks until Cycle 4

Arm type	Experimental
Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous (IV) epirubicin, 75 mg/m2 every 3 weeks for 4 cycles

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

cyclophosphamide 600 mg/m2 every 3 weeks for 4 cycles

Arm title	Herceptin

Arm description:

Epirubicin 75 mg/m2 intravenous bolus infusion and cyclophosphamide 600 mg/m2 by 30-minute IV infusion, on Day 1 of Cycle 1 and thereafter 3 weeks until Cycle 4

Arm type	Active comparator
Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous (IV) epirubicin, 75 mg/m2 every 3 weeks for 4 cycles

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

cyclophosphamide 600 mg/m2 every 3 weeks for 4 Cycles.

Number of subjects in period 1	TX05	Herceptin
Started	401	405
Completed	394	400
Not completed	7	5
Progressive disease	1	-
Protocol deviation	-	1
Decision of medical monitor	-	1
Covid-19	1	1
Adverse event, non-fatal	-	2
Consent withdrawn by subject	5	-

Period 2

Period 2 title	Treatment Period 2, Cycle 5 to Cycle 8
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Both randomization and blinding techniques were used in this study to minimize bias. This was a double-blinded study and so randomized treatment assignments were blinded to the subject, investigator/study staff and Sponsor’s study team conducting the study. The central pathology readers for pCR were also blinded to study treatment.

Arms	
Are arms mutually exclusive?	Yes
Arm title	TX05

Arm description:

TX05 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m2 administered over 60 minutes by IV infusion (Cycle 5).
TX05 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m2 administered over 60 minutes by IV infusion, on Day 1 of the treatment cycle (Cycles 6 to 8).

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/skin-prick test
Routes of administration	Intravenous use

Dosage and administration details:

TX05 8 mg/kg body weight by 90-minute IV infusion (Cycle 5). TX05 6 mg/kg body weight by 60-minute IV infusion, on Day 1 of the treatment cycle (Cycles 6 to 8).

Arm title	Herceptin

Arm description:

Herceptin 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m2 administered over 60 minutes by IV infusion (Cycle 5).
Herceptin 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m2 administered over 60 minutes by IV infusion, on Day 1 of the treatment cycle (Cycles 6 through 8).

Arm type	Active comparator
Investigational medicinal product name	Herceptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/skin-prick test
Routes of administration	Intravenous use

Dosage and administration details:

Herceptin 8 mg/kg body weight by 90-minute IV infusion (Cycle 5). Herceptin 6 mg/kg body weight by 60-minute IV infusion on Day 1 of the treatment cycle (Cycles 6 through 8).

Number of subjects in period 2	TX05	Herceptin
Started	394	400
Completed	393	393
Not completed	1	7
No information available	-	2
Covid -19	-	1
Adverse event, serious fatal	-	1
Adverse event, non-fatal	-	1
Consent withdrawn by subject	-	2
Patient decision	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period 1, Cycle 1 to Cycle 4

Reporting group description: -

Reporting group values	Treatment Period 1, Cycle 1 to Cycle 4	Total	
Number of subjects	806	806	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	662	662	
From 65-84 years	143	143	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	52.8		
standard deviation	± 11.29	-	
Gender categorical Units: Subjects			
Female	806	806	
Male	0	0	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all subjects who were randomized into the study and had received at least one dose of study drug (TX05 or Herceptin). The safety population was used for safety and immunogenicity endpoints.

Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intent-to-treat (mITT) population included all subjects who were randomized into the study and received at least 1 dose of TX05 or Herceptin. The mITT population was used for sensitivity analysis of the primary endpoint and for primary analysis of secondary endpoints.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population included all subjects who met all of the following criteria:
Randomized and receive at least one dose of study drug, either TX05 or Herceptin.
No major protocol deviations that impacted the efficacy endpoints.

An adequate sample from definitive surgical resection of their primary tumor for pathologic evaluation of residual tumor.

Reporting group values	Safety Population	mITT Population	Per Protocol Population
Number of subjects	794	794	674
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	652	652	
From 65-84 years	141	141	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	53.8	53.8	
standard deviation	± 11.32	± 11.32	±
Gender categorical			
Units: Subjects			
Female	794	794	674
Male	0	0	0

End points

End points reporting groups

Reporting group title	TX05

Reporting group description:

Epirubicin 75 mg/m2 intravenous bolus infusion and cyclophosphamide 600 mg/m2 by 30-minute IV infusion, on Day 1 of Cycle 1 and thereafter 3 weeks until Cycle 4

Reporting group title	Herceptin

Reporting group description:

Epirubicin 75 mg/m2 intravenous bolus infusion and cyclophosphamide 600 mg/m2 by 30-minute IV infusion, on Day 1 of Cycle 1 and thereafter 3 weeks until Cycle 4

Reporting group title	TX05

Reporting group description:

TX05 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m2 administered over 60 minutes by IV infusion (Cycle 5).
TX05 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m2 administered over 60 minutes by IV infusion, on Day 1 of the treatment cycle (Cycles 6 to 8).

Reporting group title	Herceptin

Reporting group description:

Herceptin 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m2 administered over 60 minutes by IV infusion (Cycle 5).
Herceptin 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m2 administered over 60 minutes by IV infusion, on Day 1 of the treatment cycle (Cycles 6 through 8).

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all subjects who were randomized into the study and had received at least one dose of study drug (TX05 or Herceptin). The safety population was used for safety and immunogenicity endpoints.

Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intent-to-treat (mITT) population included all subjects who were randomized into the study and received at least 1 dose of TX05 or Herceptin. The mITT population was used for sensitivity analysis of the primary endpoint and for primary analysis of
secondary endpoints.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population included all subjects who met all of the following criteria:
Randomized and receive at least one dose of study drug, either TX05 or Herceptin.
No major protocol deviations that impacted the efficacy endpoints.
An adequate sample from definitive surgical resection of their primary tumor for pathologic evaluation of residual tumor.

Primary: Proportion of subjects with a pathologic complete response (pCR) after the neoadjuvant chemotherapy in the per protocol (PP) population based on central lab review

End point title	Proportion of subjects with a pathologic complete response (pCR) after the neoadjuvant chemotherapy in the per protocol (PP) population based on central lab review

End point description:

To demonstrate the therapeutic equivalence of TX05 (proposed biosimilar trastuzumab) to Herceptin (trastuzumab) based on the pathologic complete response (pCR) rate following neoadjuvant chemotherapy, defined as the absence of residual invasive cancer on
hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ypT0/Tis ypN0), in subjects with HER2 positive (HER2+) invasive EBC.

End point type	Primary

End point timeframe:

After EOT/ET visit

End point values	TX05	Herceptin	Per Protocol Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	336	338	674[1]	
Units: Number of subjects	164	153	317	

Notes:

[1] - Per protocol

Statistical analyses

Statistical analysis title	pCR by Central Pathological Review
Comparison groups	TX05 v Herceptin
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Method	Asymptotic method
Parameter estimate	Risk ratio (RR)
Point estimate	1.0783
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9185
upper limit	1.2659

Notes:

[2] - The equivalence margin was determined as [0.755, 1.325] to protect 50% of the effect size based on a log scale (upper equivalence limit was exp [0.5 × ln (1.755) =1.325]).

Primary: Sensitivity analysis: Proportion of subjects with pCR in mITT by central analysis

End point title	Sensitivity analysis: Proportion of subjects with pCR in mITT by central analysis

End point description:

The combined risk ratio for trastuzumab plus chemotherapy over chemotherapy alone was estimated to be 1.755. The equivalence margin was determined as [0.755, 1.325] to protect 50% of the effect size based on a log scale (upper equivalence limit was exp [0.5 x ln (1.755)=1.325])

End point type	Primary

End point timeframe:

After EOT/ET visit

End point values	TX05	Herceptin	mITT Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	394	400	794[3]	
Units: Subjects	172	158	330	

Notes:

[3] - miTT by central analysis

Statistical analyses

Statistical analysis title	pCR by Central Pathological Review
Statistical analysis description:	
Sensitivity analysis	
Comparison groups	TX05 v Herceptin
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk ratio (RR)
Point estimate	1.1052
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9369
upper limit	1.3037

Primary: Sensitivity analysis: Proportion of subjects with pCR in mITT by local analysis

End point title	Sensitivity analysis: Proportion of subjects with pCR in mITT by local analysis
End point description:	
the combined risk ratio for trastuzumab plus chemotherapy over chemotherapy alone was estimated to be 1.755. The equivalence margin was determined as [0.755, 1.325] to protect 50% of the effect size based on a log scale (upper equivalence limit was exp [0.5 × ln (1.755) =1.325]).	
End point type	Primary
End point timeframe:	
After EOT/ET visit	

End point values	TX05	Herceptin	mITT Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	394	400	794[4]	
Units: Subjects	190	176	366	

Notes:

[4] - miTT by local analysis

Statistical analyses

Statistical analysis title	pCR in mITT by local analysis
Comparison groups	TX05 v Herceptin
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk ratio (RR)
Point estimate	1.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9427
upper limit	1.2742

Primary: Sensitivity analysis: pCR analysis in PP with stratification factors	
End point title	Sensitivity analysis: pCR analysis in PP with stratification factors
End point description:	
the combined risk ratio for trastuzumab plus chemotherapy over chemotherapy alone was estimated to be 1.755. The equivalence margin was determined as [0.755, 1.325] to protect 50% of the effect size based on a log scale (upper equivalence limit was exp [0.5 × ln (1.755) =1.325]).	
End point type	Primary
End point timeframe:	
After EOT/ET visit	

End point values	TX05	Herceptin	Per Protocol Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	336	338	674[5]	
Units: Subjects	164	153	317	

Notes:

[5] - Per protocol

Statistical analyses

Statistical analysis title	pCR analysis in PP with stratification factors
Comparison groups	TX05 v Herceptin
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	1.0842
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9283
upper limit	1.2662

Secondary: Percentage of subjects with an objective response rate (ORR) after the neoadjuvant chemotherapy in the modified intent-to-treat (mITT) population

End point title	Percentage of subjects with an objective response rate (ORR) after the neoadjuvant chemotherapy in the modified intent-to-treat (mITT) population

End point description:

End point type	Secondary

End point timeframe:

EOT/ET visit (at Week 24)

End point values	TX05	Herceptin	Per Protocol Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	394	400	794[6]	
Units: Subjects	332	340	672	

Notes:

[6] - miTT population

Statistical analyses

Statistical analysis title	Subjects with ORR in mITT population
Comparison groups	Herceptin v TX05
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk ratio (RR)
Point estimate	0.9913
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9343
upper limit	1.0519

Secondary: Percentage of subjects with positive Anti-drug antibodies (ADA) result in the safety population

End point title	Percentage of subjects with positive Anti-drug antibodies (ADA) result in the safety population

End point description:

End point type	Secondary

End point timeframe:

Baseline of Cycle 5 (Week 12), Cycle 7 (Week 18), and EOT/ET (Week 24)

End point values	TX05	Herceptin	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	347	348	695[7]	
Units: Number of subjects	4	12	16	

Notes:

[7] - Patients who were tested.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with negative ADA result in the safety population

End point title	Percentage of subjects with negative ADA result in the safety population

End point description:

End point type	Secondary

End point timeframe:

Baseline of Cycle 5 (Week 12), Cycle 7 (Week 18), and EOT/ET (Week 24)

End point values	TX05	Herceptin	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	347	348	695[8]	
Units: Number of subjects	342	336	678	

Notes:

[8] - Patients who were tested.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with positive neutralizing antibodies (NAb) result out of ADA positive samples in the safety population

End point title	Percentage of subjects with positive neutralizing antibodies (NAb) result out of ADA positive samples in the safety population

End point description:

End point type	Secondary

End point timeframe:

Baseline of Cycle 5 (Week 12), Cycle 7 (Week 18), and EOT/ET (Week 24)

End point values	TX05	Herceptin	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	347	348	695[9]	
Units: Number of subjects	0	0	0	

Notes:

[9] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with negative NAb result out of ADA positive samples in the safety population

End point title	Number of subjects with negative NAb result out of ADA positive samples in the safety population

End point description:

End point type	Secondary

End point timeframe:

Baseline of Cycle 5 (Week 12), Cycle 7 (Week 18), and EOT/ET (Week 24)

End point values	TX05	Herceptin	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	347	348	695[10]	
Units: Number of subjects	4	12	16	

Notes:

[10] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAE in cycles 5 through 8 have been summarized

Adverse event reporting additional description:

Study drug (TX05/trastuzumab) was not introduced until Cycle 5 of treatment, the analysis of AEs was focused on Cycles 5 through 8 of treatment. The following results include events that occurred on or after initiation of TX05 or Herceptin treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Safety population TX05
Reporting group description: -	
Reporting group title	Safety population Herceptin

Reporting group description: -

Serious adverse events	Safety population TX05	Safety population Herceptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 394 (2.79%)	9 / 400 (2.25%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 400 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

Foetal death			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 394 (0.25%)	0 / 400 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 394 (0.25%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 394 (0.25%)	0 / 400 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiotoxicity			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 394 (0.25%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal inflammation			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	2 / 394 (0.51%)	0 / 400 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 394 (0.00%)	2 / 400 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 394 (0.25%)	0 / 400 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 394 (0.25%)	0 / 400 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 394 (0.51%)	0 / 400 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 394 (0.25%)	1 / 400 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety population TX05	Safety population Herceptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	246 / 394 (62.44%)	250 / 400 (62.50%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	27 / 394 (6.85%)	26 / 400 (6.50%)	
occurrences (all)	31	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 394 (6.60%)	25 / 400 (6.25%)	
occurrences (all)	31	26	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	33 / 394 (8.38%)	30 / 400 (7.50%)	
occurrences (all)	40	41	
Neuropathy peripheral			
subjects affected / exposed	16 / 394 (4.06%)	33 / 400 (8.25%)	
occurrences (all)	22	38	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 394 (7.61%)	40 / 400 (10.00%)	
occurrences (all)	46	65	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	27 / 394 (6.85%)	31 / 400 (7.75%)	
occurrences (all)	55	69	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	50 / 394 (12.69%)	42 / 400 (10.50%)	
occurrences (all)	92	82	
Myalgia			
subjects affected / exposed	45 / 394 (11.42%)	39 / 400 (9.75%)	
occurrences (all)	90	81	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported