



## 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           | HU BG            |
| Global end of trial date | 27 November 2020 |

### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 02 April 2022  |
| First version publication date    | 02 April 2022  |
| Summary attachment (see zip file) | TX05-03 Results Summary (ct_result_2017-004190-13.pdf) |

### 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                  |
| Public contact               | Jennifer Lai, Tanvex Biologics Corp., +1 949 483 8507, jennifer.lai@tanvex.com |
| Scientific contact           | Jennifer Lai, Tanvex Biologics Corp., +1 949 483 8507, jennifer.lai@tanvex.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                       | 04 February 2021 |
| Is this the analysis of the primary completion data? | Yes              |
| 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<sup>2</sup>) and cyclophosphamide (600 mg/m<sup>2</sup>) 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<sup>2</sup>) 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<sup>2</sup>) 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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                         |
|--------------------------------------|-------------------------|
| 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:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| 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  $\geq$  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  |
| <b>Arm title</b>             | TX05 |

Arm description:

Epirubicin 75 mg/m<sup>2</sup> intravenous bolus infusion and cyclophosphamide 600 mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> every 3 weeks for 4 cycles

|  |  |
|--|--|
| <b>Arm title</b>   | Herceptin                                    |
| Arm description:<br>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:<br>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:<br>cyclophosphamide 600 mg/m2 every 3 weeks for 4 Cycles.   |  |

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

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 3 patients were randomized, but not treated.

## 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 |
|------------------------------|-----|

|                  |      |
|------------------|------|
| <b>Arm title</b> | TX05 |
|------------------|------|

## Arm description:

TX05 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m<sup>2</sup> administered over 60 minutes by IV infusion (Cycle 5).

TX05 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m<sup>2</sup> 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).

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Herceptin |
|------------------|-----------|

## Arm description:

Herceptin 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m<sup>2</sup> administered over 60 minutes by IV infusion (Cycle 5).

Herceptin 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m<sup>2</sup> 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         |
| Adverse event, serious fatal   | -    | 1         |
| Patient decision               | 1    | -         |
| Consent withdrawn by subject   | -    | 2         |
| Adverse event, non-fatal       | -    | 1         |
| No information available       | -    | 2         |
| Covid -19                      | -    | 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,<br>Cycle 1 to Cycle 4 | Total |  |
|---|---|-------|--|
| Number of subjects                                    | 806                                       | 806   |  |
| Age categorical<br>Units: Subjects                    |   |       |  |
| In utero  | 0   | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0   | 0     |  |
| Newborns (0-27 days)                                  | 0   | 0     |  |
| Infants and toddlers (28 days-23<br>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<br>Units: years                        |   |       |  |
| arithmetic mean                                       | 52.8                                      |       |  |
| standard deviation                                    | ± 11.29                                   | -     |  |
| Gender categorical<br>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<br>Units: Subjects  |   |   |                         |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | <br><br><br><br><br><br><br>652<br>141<br>1 | <br><br><br><br><br><br><br>652<br>141<br>1 |                         |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | <br><br>53.8<br>± 11.32                     | <br><br>53.8<br>± 11.32                     | <br><br>±               |
| Gender categorical<br>Units: Subjects   |   |   |                         |
| Female  | 794   | 794   | 674                     |
| Male  | 0   | 0   | 0                       |

## End points

### End points reporting groups

|  |                             |
|--|-----------------------------|
| Reporting group title  | TX05                        |
| Reporting group description:<br>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:<br>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:<br>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).<br>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:<br>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).<br>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:<br>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:<br>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:<br>The per protocol (PP) population included all subjects who met all of the following criteria:<br>Randomized and receive at least one dose of study drug, either TX05 or Herceptin.<br>No major protocol deviations that impacted the efficacy endpoints.<br>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 <sup>[1]</sup>      |  |
| 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 <sup>[2]</sup>         |
| 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  $\exp [0.5 \times \ln (1.755) = 1.325]$ ).

### 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  $\exp [0.5 \times \ln (1.755) = 1.325]$ )

|                      |         |
|----------------------|---------|
| 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 <sup>[3]</sup>   |  |
| 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 $\exp [0.5 \times \ln (1.755) = 1.325]$ ). |   |
| 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 <sup>[4]</sup>   |  |
| Units: Subjects             | 190             | 176             | 366                  |  |

Notes:

[4] - mITT by local analysis

## Statistical analyses

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | 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 $\exp [0.5 \times \ln (1.755) = 1.325]$ ). |
| 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 <sup>[5]</sup>      |  |
| Units: Subjects             | 164             | 153             | 317                     |  |

Notes:

[5] - Per protocol

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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   |

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

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|                 |   |
|-----------------|---|
| 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 <sup>[6]</sup>      |  |
| Units: Subjects             | 332             | 340             | 672                     |  |

Notes:

[6] - mITT population

**Statistical analyses**

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | 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                               |

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**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 <sup>[7]</sup>   |  |
| 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 <sup>[8]</sup>   |  |
| 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 <sup>[9]</sup>   |  |
| 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 <sup>[10]</sup>  |  |
| 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: -

| <b>Serious adverse events</b>                     | 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                       |  |
| 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           |  |
| 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           |  |
| 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           |  |
| 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           |  |
| 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           |  |
| 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           |  |
| 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           |  |
| 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           |  |
| 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           |  |
| 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           |  |
| 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           |  |

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

| <b>Non-serious adverse events</b>                     | Safety population<br>TX05 | Safety population<br>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                             |  |
| 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                             |  |
| Blood and lymphatic system disorders                  |                           |                                |  |
| Anaemia   |                           |                                |  |
| subjects affected / exposed                           | 26 / 394 (6.60%)          | 25 / 400 (6.25%)               |  |
| occurrences (all)                                     | 31                        | 26                             |  |
| 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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported