



Clinical trial results:

A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer

Summary

EudraCT number	2016-004019-11
Trial protocol	FR EE HU BG PL IT ES
Global end of trial date	13 January 2022

Results information

Result version number	v1 (current)
This version publication date	07 September 2025
First version publication date	07 September 2025

Trial information

Trial identification

Sponsor protocol code	TROIKA
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Prestige Biopharma Limited
Sponsor organisation address	21 Biopolis Road, #04-24 Nucleos South Building, Biopolis, Singapore, Singapore, 138567
Public contact	Sumita Pradhan, Deputy Head of Regulatory and Medical Affairs, Prestige Biopharma Limited, sumita.pradhan@prestigebio.com
Scientific contact	Jamie Kim, Head of Regulatory and Medical Affairs, Prestige Biopharma Limited, jamie.kim@prestigebio.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	14 July 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to show equivalence of the total pathological complete response rate (tpCR) in patients treated with HD201 plus chemotherapy to that in patients treated with Herceptin® plus chemotherapy. tpCR was assessed at the time of surgery after 8 cycles of neoadjuvant treatment completion.

Protection of trial subjects:

The study and clinical study protocols were reviewed and approved by Independent Ethics Committee (IEC) for each study centre.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013) and that are consistent with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines (ICH E6) and applicable local regulatory requirements and laws.

The nature and purpose of the study was fully explained to each patient and written informed consent was obtained at Screening from each patient before any study related procedures were performed. The consent documents for the study were reviewed and approved by the appropriate IEC or IRB prior to use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Belarus: 27
Country: Number of subjects enrolled	Georgia: 40
Country: Number of subjects enrolled	Malaysia: 18

Country: Number of subjects enrolled	Russian Federation: 302
Country: Number of subjects enrolled	Thailand: 21
Country: Number of subjects enrolled	Ukraine: 67
Worldwide total number of subjects	503
EEA total number of subjects	28

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)	423
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 625 patients were screened between 19 February and 21 September 2018 across 70 centers in 12 countries and constitute the Total Set. 503 were randomised (251 to HD201 group and 252 to Herceptin® group) and 502 were treated and constitute the mFAS set (250 in HD201 group and 252 in Herceptin® group).

Pre-assignment

Screening details:

Key IC: HER2 overexpressed, non-metastatic, unilateral, newly diagnoses, operable early breast cancer of clinical stage II and III, including inflammatory breast cancer, histologically confirmed primary invasive carcinoma of the breast.

Key EC: metastatic (stage IV) except supraclavicular nodes, bilateral or multicentric breast cancer.

Period 1

Period 1 title	Treatment period (overall period)
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	HD201

Arm description:

Patients received HD201 every 3 weeks for 18 cycles (8 cycles of neoadjuvant treatment in combination with chemotherapy and 10 cycles of adjuvant therapy).

Arm type	Experimental
Investigational medicinal product name	HD201
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose regimen for neoadjuvant period: 8 mg/kg over 90 min (loading dose – Cycle 1), then 6 mg/kg over 60 min (maintenance dose – Cycle 2), then 6 mg/kg over 30 min every 3 weeks (maintenance dose –Cycles 2 to 8).

Dose regimen for adjuvant period: 8 mg/kg over 90 min (loading dose – Cycle 9), then 6 mg/kg over 30 min (maintenance dose – Cycles 10 to 18) every 3 weeks.

Arm title	Herceptin®
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Arm description:

Patients received Herceptin® every 3 weeks for 18 cycles (8 cycles of neoadjuvant treatment in combination with chemotherapy and 10 cycles of adjuvant therapy).

Arm type	Active comparator
Investigational medicinal product name	Herceptin®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose regimen for neoadjuvant period: 8 mg/kg over 90 min (loading dose – Cycle 1), then 6 mg/kg over 60 min (maintenance dose – Cycle 2), then 6 mg/kg over 30 min every 3 weeks (maintenance dose –Cycles 2 to 8).

Dose regimen for adjuvant period: 8 mg/kg over 90 min (loading dose – Cycle 9), then 6 mg/kg over 30 min (maintenance dose – Cycles 10 to 18) every 3 weeks.

Number of subjects in period 1^[1]	HD201	Herceptin®
Started	250	252
Completed	222	228
Not completed	28	24
Adverse event/other	4	4
Physician decision	-	1
Progressive disease/adverse event	7	5
Withdrawal by patient/non-compliance	5	8
Adverse event/physician decision	-	2
Adverse event/intercurrent illness	2	1
Death	4	-
Adverse event	1	1
Adverse event/progressive disease	1	-
Progressive disease	2	2
Refusal/did not appear for surgery	2	-

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: One of the 503 patients was randomised by error at screening. After randomization to the HD201 treatment group, it appeared that the patient was a screen failure since she suffered from metastatic breast cancer.

The remaining 502 patients, 250 in the HD201 treatment group and 252 in the Herceptin® treatment group, were all treated and constituted the mFAS.

Baseline characteristics

Reporting groups

Reporting group title	HD201
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Reporting group description:

Patients received HD201 every 3 weeks for 18 cycles (8 cycles of neoadjuvant treatment in combination with chemotherapy and 10 cycles of adjuvant therapy).

Reporting group title	Herceptin®
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Reporting group description:

Patients received Herceptin® every 3 weeks for 18 cycles (8 cycles of neoadjuvant treatment in combination with chemotherapy and 10 cycles of adjuvant therapy).

Reporting group values	HD201	Herceptin®	Total
Number of subjects	250	252	502
Age categorical Units: Subjects			
Adults (18-64 years)	210	212	422
From 65-84 years	40	40	80
Age continuous Units: years			
median	53.69	54.21	
standard deviation	± 11.52	± 11.41	-
Gender categorical Units: Subjects			
Female	250	252	502

End points

End points reporting groups

Reporting group title	HD201
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Reporting group description:

Patients received HD201 every 3 weeks for 18 cycles (8 cycles of neoadjuvant treatment in combination with chemotherapy and 10 cycles of adjuvant therapy).

Reporting group title	Herceptin®
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Reporting group description:

Patients received Herceptin® every 3 weeks for 18 cycles (8 cycles of neoadjuvant treatment in combination with chemotherapy and 10 cycles of adjuvant therapy).

Subject analysis set title	PPS
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Subject analysis set type	Per protocol
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Subject analysis set description:

All patients of the mFAS who received neoadjuvant and adjuvant study medication according to the protocol, without any major protocol deviation impacting the primary efficacy assessment, and who had surgery after completion of neoadjuvant treatment or did not undergo surgery due to lack of efficacy.

Protocol deviations were assessed during a pre-analysis review meeting that was held before database lock.

Subject analysis set title	SAF
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All patients of the FAS who received at least one dose of neoadjuvant study medication (HD201 or Herceptin®)

Primary: Total pathological complete response (tpCR)

End point title	Total pathological complete response (tpCR)
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End point description:

Complete absence of cancer cells in the breast and in the axillary lymph nodes (ypT0/is, ypN0) assessed locally in specimen obtained during surgery

End point type	Primary
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End point timeframe:

At the time of surgery after 8 cycles of neoadjuvant treatment completion.

End point values	HD201	Herceptin®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	236		
Units: Percentage				
arithmetic mean (confidence interval 95%)	49.8 (42.7 to 56.8)	51.9 (45.0 to 58.7)		

Statistical analyses

Statistical analysis title	Risk Difference Analysis for tpCR in PPS
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Statistical analysis description:

To show the equivalence in terms of the tpCR rate between HD201 and Herceptin® within pre-defined equivalence margins, which was set to [-15% ; 15%] in this study.

Comparison groups	HD201 v Herceptin®
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.6
upper limit	7.5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) are reported for the entire treatment period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	HD201
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Reporting group description:

Patients received HD201 every 3 weeks for 18 cycles (8 cycles of neoadjuvant treatment in combination with chemotherapy and 10 cycles of adjuvant therapy).

Reporting group title	Herceptin®
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Reporting group description:

Patients received Herceptin® every 3 weeks for 18 cycles (8 cycles of neoadjuvant treatment in combination with chemotherapy and 10 cycles of adjuvant therapy).

Serious adverse events	HD201	Herceptin®	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 250 (9.60%)	17 / 252 (6.75%)	
number of deaths (all causes)	7	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
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			

Sudden death			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 250 (0.80%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Colpocele			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			

subjects affected / exposed	2 / 250 (0.80%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiorespiratory arrest			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytotoxic cardiomyopathy			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 250 (0.80%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	6 / 250 (2.40%)	4 / 252 (1.59%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 250 (0.80%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 250 (0.40%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Open angle glaucoma			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 250 (0.80%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 250 (0.00%)	3 / 252 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 250 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Opisthorchiasis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (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			
Hyperglycaemia			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 250 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	HD201	Herceptin®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	226 / 250 (90.40%)	230 / 252 (91.27%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	35 / 250 (14.00%)	41 / 252 (16.27%)	
occurrences (all)	52	60	
Aspartate aminotransferase increased			
subjects affected / exposed	37 / 250 (14.80%)	31 / 252 (12.30%)	
occurrences (all)	52	54	
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 250 (7.60%)	29 / 252 (11.51%)	
occurrences (all)	25	45	
Neutrophil count decreased			
subjects affected / exposed	15 / 250 (6.00%)	8 / 252 (3.17%)	
occurrences (all)	23	12	
Blood alkaline phosphatase increased			
subjects affected / exposed	15 / 250 (6.00%)	24 / 252 (9.52%)	
occurrences (all)	23	38	
Ejection fraction decreased			
subjects affected / exposed	21 / 250 (8.40%)	21 / 252 (8.33%)	
occurrences (all)	22	22	
Electrocardiogram abnormal			
subjects affected / exposed	16 / 250 (6.40%)	9 / 252 (3.57%)	
occurrences (all)	21	9	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	36 / 250 (14.40%)	44 / 252 (17.46%)	
occurrences (all)	37	49	
Radiation skin injury			
subjects affected / exposed	16 / 250 (6.40%)	16 / 252 (6.35%)	
occurrences (all)	16	16	
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	11 / 250 (4.40%) 11	16 / 252 (6.35%) 21	
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	16 / 250 (6.40%) 17	16 / 252 (6.35%) 17	
Mitral valve incompetence subjects affected / exposed occurrences (all)	10 / 250 (4.00%) 10	14 / 252 (5.56%) 16	
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	12 / 250 (4.80%) 12	13 / 252 (5.16%) 13	
Headache subjects affected / exposed occurrences (all)	26 / 250 (10.40%) 33	22 / 252 (8.73%) 30	
Dysgeusia subjects affected / exposed occurrences (all)	9 / 250 (3.60%) 14	13 / 252 (5.16%) 25	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	68 / 250 (27.20%) 235	66 / 252 (26.19%) 210	
Fatigue subjects affected / exposed occurrences (all)	62 / 250 (24.80%) 117	67 / 252 (26.59%) 104	
Oedema peripheral subjects affected / exposed occurrences (all)	17 / 250 (6.80%) 26	14 / 252 (5.56%) 14	
Pyrexia subjects affected / exposed occurrences (all)	17 / 250 (6.80%) 20	13 / 252 (5.16%) 15	
Blood and lymphatic system disorders Neutropenia			

subjects affected / exposed occurrences (all)	76 / 250 (30.40%) 142	77 / 252 (30.56%) 137	
Anaemia subjects affected / exposed occurrences (all)	70 / 250 (28.00%) 111	61 / 252 (24.21%) 90	
Leukopenia subjects affected / exposed occurrences (all)	44 / 250 (17.60%) 82	51 / 252 (20.24%) 92	
Hyperglobulinaemia subjects affected / exposed occurrences (all)	14 / 250 (5.60%) 36	13 / 252 (5.16%) 27	
Thrombocytopenia subjects affected / exposed occurrences (all)	13 / 250 (5.20%) 21	10 / 252 (3.97%) 11	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	86 / 250 (34.40%) 238	93 / 252 (36.90%) 235	
Diarrhoea subjects affected / exposed occurrences (all)	45 / 250 (18.00%) 73	45 / 252 (17.86%) 66	
Vomiting subjects affected / exposed occurrences (all)	21 / 250 (8.40%) 33	18 / 252 (7.14%) 26	
Stomatitis subjects affected / exposed occurrences (all)	19 / 250 (7.60%) 23	14 / 252 (5.56%) 22	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	202 / 250 (80.80%) 202	200 / 252 (79.37%) 200	
Rash subjects affected / exposed occurrences (all)	26 / 250 (10.40%) 43	17 / 252 (6.75%) 30	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	40 / 250 (16.00%)	31 / 252 (12.30%)	
occurrences (all)	65	57	
Bone pain			
subjects affected / exposed	19 / 250 (7.60%)	16 / 252 (6.35%)	
occurrences (all)	36	46	
Myalgia			
subjects affected / exposed	16 / 250 (6.40%)	19 / 252 (7.54%)	
occurrences (all)	23	27	
Metabolism and nutrition disorders			
Hypoproteinaemia			
subjects affected / exposed	20 / 250 (8.00%)	17 / 252 (6.75%)	
occurrences (all)	39	33	
Hypocalcaemia			
subjects affected / exposed	14 / 250 (5.60%)	15 / 252 (5.95%)	
occurrences (all)	26	25	
Decreased appetite			
subjects affected / exposed	13 / 250 (5.20%)	12 / 252 (4.76%)	
occurrences (all)	19	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2018	The following changes were implemented in the first protocol amendment: • Dual ISH (DISH) test was added to the inclusion criteria to assess overexpression of HER2+. • Section on blinding was updated to indicate that the pharmacists were only partially blinded, not blinded. • Details were added on dosing regimen, period (neoadjuvant, surgery, adjuvant), treatment cycle and treatment duration.
26 April 2018	The following changes were implemented in the local protocol amendment for France: • The following exclusion criteria were added (EC 19 to 22): - o Patients with stage 1 breast cancer. - o Patients with acute urinary tract infection or pre-existing haemorrhagic cystitis. - o Patients who have received live attenuated vaccines. - o Patients who have received prohibited drugs.
01 October 2018	The following changes were implemented in the second protocol amendment: • Planned completion of recruitment changed from Q2 2018 to Q3 2018, planned end of study changed from Q4 2021 to Q1 2022, and analysis of primary endpoint changed from Q4 2018 to Q1 2019. • Timepoints were added for the collection of immunogenicity samples to include Cycle 5 (this sample was to only be tested if pre-surgery sample was ADA-positive), post-surgery (before Cycle 10), and before Cycle 14. • Addition of NAb testing, in which only ADA-positive samples were to be tested for NAb • Section on PK analysis was updated with a change in the number of patients required for PK analysis. While PK samples were taken for all the patients that were randomised to treatment on cycle 5 and 8, PK testing was only performed on the first 320 patient samples to obtain values for approximately 150 patients in each treatment group. The remaining samples were to be stored for potential future analysis. • IHC2+/DISH+ was added to define HER2 positive tumours • Timing of central reading of tpCR was altered to "to be performed at a later stage". To be noted that central reading of tpCR occurred after unblinding.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported