



Clinical trial results:

A Phase III Randomised, Double-Blind, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB3 (proposed trastuzumab biosimilar) and Herceptin® in Women with Newly Diagnosed HER2 Positive Early or Locally Advanced Breast Cancer in Neoadjuvant Setting

Summary

EudraCT number	2013-004172-35
Trial protocol	CZ PL BG RO
Global end of trial date	17 January 2017

Results information

Result version number	v1 (current)
This version publication date	25 January 2019
First version publication date	25 January 2019

Trial information

Trial identification

Sponsor protocol code	SB3-G31-BC
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02149524
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Samsung Bioepis Co., Ltd.
Sponsor organisation address	107, Cheomdan-daero, Incheon, Korea, Republic of,
Public contact	Quintiles Contact Centre, Quintiles Limited, 001 8622613634,
Scientific contact	Quintiles Contact Centre, Quintiles Limited, 001 8622613634,

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	17 January 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate comparable clinical efficacy of SB3 to Herceptin®, in terms of Pathologic complete response rate of the primary breast tumour in women with HER2 positive Early breast cancer or Locally advanced breast cancer in neoadjuvant setting.

Protection of trial subjects:

The study and clinical study protocols were reviewed and approved by Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2008) and that are consistent with International Conference on Harmonisation (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 subject and written informed consent was obtained at Screening from each subject before any study related procedures were performed. The consent documents for the study was reviewed and approved by the appropriate IEC or IRB prior to use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 74
Country: Number of subjects enrolled	Malaysia: 21
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Philippines: 52
Country: Number of subjects enrolled	Vietnam: 16
Country: Number of subjects enrolled	Bosnia and Herzegovina: 7
Country: Number of subjects enrolled	Ukraine: 166
Country: Number of subjects enrolled	India: 104
Country: Number of subjects enrolled	Russian Federation: 211
Country: Number of subjects enrolled	Poland: 143
Country: Number of subjects enrolled	Romania: 40
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	France: 19

Worldwide total number of subjects	875
EEA total number of subjects	223

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)	856
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who fulfilled the inclusion/exclusion criteria were randomly assigned to 1 of the 2 treatments of this study.

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SB3 (proposed trastuzumab biosimilar)

Arm description:

Participants received SB3 every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy).

Arm type	Experimental
Investigational medicinal product name	SB3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SB3 was administered intravenously at a loading dose of 8 mg/kg and at a maintenance dose of 6 mg/kg for the subsequent cycles.

Arm title	Herceptin
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Arm description:

Participants received EU sourced Herceptin® every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy)

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

Dosage and administration details:

Herceptin was administered intravenously at a loading dose of 8 mg/kg and at a maintenance dose of 6 mg/kg for the subsequent cycles.

Number of subjects in period 1	SB3 (proposed trastuzumab biosimilar)	Herceptin
Started	437	438
Completed	380	384
Not completed	57	54
Adverse event, serious fatal	1	5
Consent withdrawn by subject	10	9
Administrative or other reasons	4	2
Adverse event, non-fatal	13	12
Progressive disease/disease recurrence	23	22
Lost to follow-up	5	4
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	SB3 (proposed trastuzumab biosimilar)
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Reporting group description:

Participants received SB3 every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy).

Reporting group title	Herceptin
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Reporting group description:

Participants received EU sourced Herceptin® every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy)

Reporting group values	SB3 (proposed trastuzumab biosimilar)	Herceptin	Total
Number of subjects	437	438	875
Age categorical Units: Subjects			
Less than 60 years			0
60 years and over			0
Age continuous Units: years arithmetic mean standard deviation	49.5 ± 9.51	49.6 ± 9.38	-
Gender categorical Units: Subjects			
Female	437	438	875
Male	0	0	0

End points

End points reporting groups

Reporting group title	SB3 (proposed trastuzumab biosimilar)
Reporting group description:	
Participants received SB3 every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy).	
Reporting group title	Herceptin
Reporting group description:	
Participants received EU sourced Herceptin® every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy)	
Subject analysis set title	Per-protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPS consisted of all FAS subjects who completed the 8 cycles of neoadjuvant therapy and surgery. The PPS was the primary analysis set. Major protocol deviations that led to exclusion from this set were pre-specified prior to unblinding the treatment codes for analyses. Subjects who did not have a pathological response assessment were excluded from the PPS.	

Primary: bpCR

End point title	bpCR
End point description:	
pCR was defined as no histological evidence of residual invasive tumour cells in the breast specimen removed at surgery [breast pCR; bpCR]. Non-invasive breast residuals were allowed and the pathological examination of axillary lymph nodes was not to be considered; ypT0/is, ypN0/+.	
End point type	Primary
End point timeframe:	
Week 24	

End point values	SB3 (proposed trastuzumab biosimilar)	Herceptin	Per-protocol set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	402	398	800 ^[1]	
Units: percentage				
number (not applicable)	51.7	42.0	800	

Notes:

[1] - SB3: 402/Herceptin: 398

Statistical analyses

Statistical analysis title	bpCR (per-protocol analysis)
Comparison groups	SB3 (proposed trastuzumab biosimilar) v Herceptin
Number of subjects included in analysis	800
Analysis specification	Pre-specified
Analysis type	equivalence ^[2]
Parameter estimate	Risk ratio (RR)
Point estimate	1.259

Confidence interval	
level	90 %
sides	2-sided
lower limit	1.112
upper limit	1.426

Notes:

[2] - - Equivalence margin: [0.785, 1.546]

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) and serious AEs (SAEs) were reported from the time the participant had taken at least 1 dose of study drug and the time of informed consent (TEAEs), respectively, through 30 days after the last dose of study drug (EOS).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	SB3 (proposed trastuzumab biosimilar)
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Reporting group description:

Participants received SB3 every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy).

Reporting group title	Herceptin
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Reporting group description:

Participants received EU sourced Herceptin every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy).

Serious adverse events	SB3 (proposed trastuzumab biosimilar)	Herceptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 437 (12.81%)	58 / 438 (13.24%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 437 (0.23%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian hyperstimulation syndrome			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			

subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 437 (0.23%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hallucination, auditory			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			

subjects affected / exposed	8 / 437 (1.83%)	4 / 438 (0.91%)	
occurrences causally related to treatment / all	0 / 20	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 437 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 437 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation mucositis			

subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	3 / 437 (0.69%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 437 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			

subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	10 / 437 (2.29%)	13 / 438 (2.97%)	
occurrences causally related to treatment / all	1 / 11	1 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	7 / 437 (1.60%)	5 / 438 (1.14%)	
occurrences causally related to treatment / all	2 / 7	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 437 (0.46%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 437 (0.69%)	3 / 438 (0.68%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 437 (0.46%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 437 (0.23%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastritis	subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids	subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders				
Hepatic function abnormal	subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
	occurrences causally related to treatment / all	1 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders				
Renal failure acute	subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders				
Myalgia	subjects affected / exposed	2 / 437 (0.46%)	0 / 438 (0.00%)	
	occurrences causally related to treatment / all	1 / 2	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture	subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations				
Pneumonia	subjects affected / exposed	4 / 437 (0.92%)	0 / 438 (0.00%)	
	occurrences causally related to treatment / all	0 / 5	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection				

subjects affected / exposed	2 / 437 (0.46%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 437 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 437 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 437 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 437 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 437 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 437 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraspinal abscess			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 437 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 437 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 437 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 437 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SB3 (proposed trastuzumab biosimilar)	Herceptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	420 / 437 (96.11%)	414 / 438 (94.52%)	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	84 / 437 (19.22%)	83 / 438 (18.95%)	
occurrences (all)	150	150	
Aspartate aminotransferase increased			
subjects affected / exposed	68 / 437 (15.56%)	63 / 438 (14.38%)	
occurrences (all)	102	110	
Neutrophil count decreased			
subjects affected / exposed	53 / 437 (12.13%)	53 / 438 (12.10%)	
occurrences (all)	124	162	
White blood cell count decreased			
subjects affected / exposed	25 / 437 (5.72%)	32 / 438 (7.31%)	
occurrences (all)	69	71	
Blood alkaline phosphatase increased			
subjects affected / exposed	22 / 437 (5.03%)	29 / 438 (6.62%)	
occurrences (all)	40	43	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	48 / 437 (10.98%)	38 / 438 (8.68%)	
occurrences (all)	48	47	
Procedural pain			
subjects affected / exposed	39 / 437 (8.92%)	53 / 438 (12.10%)	
occurrences (all)	41	54	
Infusion related reaction			
subjects affected / exposed	37 / 437 (8.47%)	42 / 438 (9.59%)	
occurrences (all)	53	62	
Postoperative wound complication			
subjects affected / exposed	27 / 437 (6.18%)	21 / 438 (4.79%)	
occurrences (all)	27	21	
Vascular disorders			
Lymphorrhoea			
subjects affected / exposed	32 / 437 (7.32%)	30 / 438 (6.85%)	
occurrences (all)	58	51	
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 437 (7.09%)	32 / 438 (7.31%)	
occurrences (all)	55	51	
Peripheral sensory neuropathy			

subjects affected / exposed occurrences (all)	30 / 437 (6.86%) 42	23 / 438 (5.25%) 40	
Neuropathy peripheral subjects affected / exposed occurrences (all)	22 / 437 (5.03%) 24	12 / 438 (2.74%) 12	
Psychiatric disorders subjects affected / exposed occurrences (all)	22 / 437 (5.03%) 32	22 / 438 (5.02%) 31	
Insomnia subjects affected / exposed occurrences (all)	22 / 437 (5.03%) 32	22 / 438 (5.02%) 31	
Blood and lymphatic system disorders			
Neutropenia subjects affected / exposed occurrences (all)	239 / 437 (54.69%) 654	280 / 438 (63.93%) 634	
Leukopenia subjects affected / exposed occurrences (all)	125 / 437 (28.60%) 259	113 / 438 (25.80%) 237	
Anaemia subjects affected / exposed occurrences (all)	96 / 437 (21.97%) 180	95 / 438 (21.69%) 198	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	88 / 437 (20.14%) 186	79 / 438 (18.04%) 182	
Asthenia subjects affected / exposed occurrences (all)	57 / 437 (13.04%) 145	55 / 438 (12.56%) 162	
Pyrexia subjects affected / exposed occurrences (all)	39 / 437 (8.92%) 50	37 / 438 (8.45%) 48	
Oedema peripheral subjects affected / exposed occurrences (all)	18 / 437 (4.12%) 27	31 / 438 (7.08%) 34	
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	143 / 437 (32.72%) 362	135 / 438 (30.82%) 388	
Diarrhoea subjects affected / exposed occurrences (all)	91 / 437 (20.82%) 143	65 / 438 (14.84%) 90	
Stomatitis subjects affected / exposed occurrences (all)	61 / 437 (13.96%) 107	51 / 438 (11.64%) 88	
Vomiting subjects affected / exposed occurrences (all)	61 / 437 (13.96%) 110	50 / 438 (11.42%) 87	
Dyspepsia subjects affected / exposed occurrences (all)	26 / 437 (5.95%) 39	22 / 438 (5.02%) 27	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	41 / 437 (9.38%) 46	27 / 438 (6.16%) 34	
Oropharyngeal pain subjects affected / exposed occurrences (all)	25 / 437 (5.72%) 28	19 / 438 (4.34%) 22	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	299 / 437 (68.42%) 349	283 / 438 (64.61%) 324	
Rash subjects affected / exposed occurrences (all)	47 / 437 (10.76%) 61	45 / 438 (10.27%) 62	
Nail disorder subjects affected / exposed occurrences (all)	22 / 437 (5.03%) 23	23 / 438 (5.25%) 23	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	63 / 437 (14.42%) 148	66 / 438 (15.07%) 138	

Arthralgia			
subjects affected / exposed	48 / 437 (10.98%)	47 / 438 (10.73%)	
occurrences (all)	74	70	
Joint range of motion decreased			
subjects affected / exposed	27 / 437 (6.18%)	20 / 438 (4.57%)	
occurrences (all)	33	21	
Bone pain			
subjects affected / exposed	23 / 437 (5.26%)	24 / 438 (5.48%)	
occurrences (all)	39	39	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	44 / 437 (10.07%)	40 / 438 (9.13%)	
occurrences (all)	66	64	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	40 / 437 (9.15%)	41 / 438 (9.36%)	
occurrences (all)	78	103	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2014	<ul style="list-style-type: none">Text was added to the section on administration of neoadjuvant chemotherapy to be in line with the French regulatory authority's recommendation.Administrative changes were made.
08 July 2014	<ul style="list-style-type: none">Three exclusion criteria were clarified.To avoid repetition of procedures at Screening, an update was made to allow results from previous assessments (even if they had occurred before the signing of informed consent) to be used as screening procedures as long as they were within 28 days of randomisation.Text was clarified and editorial/administrative changes were implemented where appropriate.
26 August 2014	<ul style="list-style-type: none">The period that women of childbearing potential had to agree to use contraception was increased from 6 to 7 months in line with updated SmPC for Herceptin®.Results from a bilateral mammography performed within 6 weeks before randomisation was now acceptable as a screening procedure because significant changes in a few weeks were unlikely.A definition of disease stage when tumour size was 2.0 cm (T1) was added to the stratification factors.A paragraph on pooling data from centres for the efficacy analysis was deleted because subjects were randomised by country not centre.The axillary staging procedures were updated in accordance with recent breast surgery guidelines.Text was further clarified and editorial/administrative changes were implemented where appropriate.
17 December 2014	<ul style="list-style-type: none">Determination of sample size and its rationale was updated as a result of newly found literature and references added to the bibliography [Chang, 2008]. The expected bpCR rate was changed from 40% to 37.5%, the number of evaluable subjects to meet an 80% power changed from 220 to 358 subjects per arm and the equivalence margin changed from within 15% to 0.785 to 1.546. The number of subjects to be randomised was therefore changed from 249 to 403 per arm and the expected dropout rate changed from 12% to 11%.The number of subjects to be randomised was increased from 498 to 806 and the expected recruitment period increased from 12 to 15 months.The criteria for declaring equivalence between the two treatments (primary efficacy endpoint) was modified: From: Equivalence between the two treatment groups will be declared if the two-sided 95% (CI) of the difference in the pCR rate between treatments is entirely contained within the equivalence margin of [-15%, 15%]. The two-sided 95% CI of the difference will be estimated for the PPS. To: To demonstrate equivalence in the pCR rate between the two treatment groups in accordance with both FDA and EMA recommendation, the ratio and the difference in pCR rate will be analysed for the primary analysis. Equivalence will be declared if the two-sided 95% (CI) of the ratio in the pCR rate between treatments is entirely contained within the equivalence margin of [0.785, 1.546] or, if the 95% CI of the difference in the pCR rate between treatments is entirely contained within the equivalence margin of [-13%, 13%]. The 95% CIs of the difference will be estimated for the PPS. The difference of pCR will be used for EMA submission and the relative ratio of pCR will be used for FDA submission.

23 April 2015	<ul style="list-style-type: none"> • References (different versions of NCI-CTCAE) to be used to grade the severity of AEs of CHF, left ventricular dysfunction and febrile neutropenia were added. • Sample size for PK Population was amended from 270 (135 per arm) to 300 subjects (150 per arm). The expected non-evaluable rate was updated from 22% to 30%. • Clarifications were made to PK sample procedures. • More detail and clarification was added to the sections on dose modification and delays of IP and non-IP. • Premature withdrawal criteria were updated with regard to allowed treatment delays. • In Appendix 4 of the protocol, a section was added on quality control of pCR by central review. • In the case of high-risk subjects, G-CSF was allowed as a primary prophylaxis for neutropenic events. • Text was further clarified and editorial/administrative changes were implemented where appropriate.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29373094>

<http://www.ncbi.nlm.nih.gov/pubmed/29448072>