Clinical trial results:
A Randomized, Open Label, Multicenter Phase IIIb Study Comparing Two Trastuzumab Dosing Regimens, Each in Combination With Cisplatin/Capecitabine Chemotherapy, as First-Line Therapy in Patients With HER2-Positive Metastatic Gastric or Gastro-Esophageal Junction Adenocarcinoma Who Have Not Received Prior Treatment for Metastatic Disease

Summary

EudraCT number	2011-001526-19
Trial protocol	DE ES GB IT CZ HU PT PL
Global end of trial date	25 August 2015

Results information

Result version number	v1 (current)
This version publication date	22 October 2016
First version publication date	22 October 2016

Trial information

Trial identification

Sponsor protocol code	BO27798

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01450696
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 August 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study was designed to evaluate the effect of Herceptin (trastuzumab) administered at a loading dose of 8 milligrams per kilogram (mg/kg) followed by 6 mg/kg every three weeks (q3w) as standard of care versus a loading dose of Herceptin at 8 mg/kg followed by 10 mg/kg along with cisplatin and capecitabine, to test whether it produced higher trastuzumab exposure and might have resulted in improved survival duration.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Bosnia and Herzegovina: 16
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	China: 77
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 13
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Peru: 7

Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	Turkey: 38
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	296
EEA total number of subjects	39

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)	170
From 65 to 84 years	125
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 248 participants (124 participants per group) were randomized in the study up to data cutoff date of 13 February 2015, and 48 additional participants (24 participants per group) were randomized between data cutoff date of 13 February 2015 and end of study (25 August 2015) for additional safety data.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Capecitabine + Cisplatin + Herceptin (6 mg/kg)

Arm description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg every three weeks (q3w) as standard of care from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 milligrams per meter-squared (mg/m^2) intravenously q3w plus capecitabine 800 mg/m^2 orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

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

Dosage and administration details:

Herceptin was administered IV at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg or 10 mg/kg (depending upon treatment assignment) q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

Arm title	Capecitabine + Cisplatin + Herceptin (10 mg/kg)

Arm description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 10 mg/kg q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m^2 intravenously q3w plus capecitabine 800 mg/m^2 orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

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

Dosage and administration details:

Herceptin was administered IV at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg or 10 mg/kg (depending upon treatment assignment) q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

Number of subjects in period 1	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)
Started	148	148
Treated (Safety Population)	147	147
Completed	0	0
Not completed	148	148
Consent withdrawn by subject	13	2
Study terminated by Sponsor	53	58
Death	77	84
Non-compliance	1	-
Never treated	1	1
Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Capecitabine + Cisplatin + Herceptin (6 mg/kg)
Reporting group description:	
Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg every three weeks (q3w) as standard of care from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 milligrams per meter-squared (mg/m^2) intravenously q3w plus capecitabine 800 mg/m^2 orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).	
Reporting group title	Capecitabine + Cisplatin + Herceptin (10 mg/kg)
Reporting group description:	
Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 10 mg/kg q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m^2 intravenously q3w plus capecitabine 800 mg/m^2 orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).	

Reporting group values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)	Total
Number of subjects	148	148	296
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 59.5 ± 10.6	 62.4 ± 10.7	 -
Gender categorical Units: Subjects			
Female	32	37	69
Male	116	111	227

End points

End points reporting groups

Reporting group title	Capecitabine + Cisplatin + Herceptin (6 mg/kg)

Reporting group description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg every three weeks (q3w) as standard of care from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 milligrams per meter-squared (mg/m^2) intravenously q3w plus capecitabine 800 mg/m^2 orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

Reporting group title	Capecitabine + Cisplatin + Herceptin (10 mg/kg)

Reporting group description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 10 mg/kg q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m^2 intravenously q3w plus capecitabine 800 mg/m^2 orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

Primary: Percentage of Participants Who Died - Full Analysis Set (FAS)

End point title	Percentage of Participants Who Died - Full Analysis Set (FAS)[1]

End point description:

The percentage of participants who died as of the analysis data cutoff date of 13 February 2015 was reported among participants from the FAS with available data. The FAS population included all participants who were randomized in this study. Here, number of subjects analyzed reflects the number of participants who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

From date of randomization until death or premature withdrawal (up to approximately 31 months or data cutoff date of 13 February 2015)

Notes:

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

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	124		
Units: percentage of participants				
number (not applicable)	46.8	54		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival - FAS

End point title	Overall Survival - FAS

End point description:

Overall survival was defined as the time from the date of randomization to the date of death from any cause. Overall survival was estimated among participants from the FAS using the Kaplan-Meier approach. The 95 percent (%) confidence interval (CI) for median was computed using the method of Brookmeyer and Crowley. FAS population. Here, number of participants analyzed reflects the number of participants who were evaluable for this outcome measure.

End point type	Primary

End point timeframe:

From date of randomization until death or premature withdrawal (up to approximately 31 months or data cutoff date of 13 February 2015)

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	124		
Units: months				
median (confidence interval 95%)	12.485 (10.086 to 13.864)	10.612 (9.363 to 12.419)		

Statistical analyses

Statistical analysis title	Stratified Analysis

Statistical analysis description:

Stratified analysis included stratum of creatinine clearance (45 to 59 milliliters per minute [mL/min] and greater than or equal to [≥] 60 mL/min). Hazard ratio was estimated by Cox regression.

Comparison groups	Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg)
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2401
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.78

Statistical analysis title	Unstratified Analysis

Statistical analysis description:

Unstratified analysis. Hazard ratio was estimated by Cox regression.

Comparison groups	Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg)

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1285
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.88

Secondary: Percentage of Participants Who Died - Per Protocol Set (PPS)

End point title	Percentage of Participants Who Died - Per Protocol Set (PPS)

End point description:

The percentage of participants who died as of the analysis data cutoff date of 13 February 2015 was reported among participants from the PPS. The PPS included all participants who were found to have a trastuzumab minimum plasma concentration (Cmin) less than (<) 12 micrograms per milliliter (µg/mL) on treatment Day 21 of Cycle 1 following the initial loading dose of 8 mg/kg.

End point type	Secondary

End point timeframe:

From date of randomization until death or premature withdrawal (up to approximately 31 months or data cutoff date of 13 February 2015)

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: percentage of participants				
number (not applicable)	51.5	59.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - PPS

End point title	Overall Survival - PPS

End point description:

Overall survival was defined as the time from the date of randomization to the date of death from any cause. Overall survival was estimated among participants from the PPS using the Kaplan-Meier approach. The 95% CI for median was computed using the method of Brookmeyer and Crowley. PPS population.

End point type	Secondary

End point timeframe:

From date of randomization until death or premature withdrawal (up to approximately 31 months or data cutoff date of 13 February 2015)

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: months				
median (confidence interval 95%)	10.809 (8.082 to 14.752)	9.363 (5.552 to 14.357)		

Statistical analyses

Statistical analysis title	Stratified Analysis

Statistical analysis description:

Stratified analysis included stratum of creatinine clearance (45 to 59 mL/min and ≥60 mL/min). Hazard ratio was estimated by Cox regression.

Comparison groups	Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg)
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9931
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2.04

Statistical analysis title	Unstratified Analysis

Statistical analysis description:

Unstratified analysis. Hazard ratio was estimated by Cox regression.

Comparison groups	Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg)

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9458
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	2.02

Secondary: Percentage of Participants With Disease Progression or Death - PPS

End point title	Percentage of Participants With Disease Progression or Death - PPS

End point description:

Disease progression was defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as a ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including Baseline (nadir). In addition to the relative increase of 20%, the sum was also required to demonstrate an absolute increase of ≥5 millimeters (mm). The percentage of participants who died or experienced disease progression as of the analysis data cutoff date of 13 February 2015 was reported among participants from the PPS. PPS population.

End point type	Secondary

End point timeframe:

From date of randomization until first occurrence of disease progression or death; assessed every 6 weeks (up to approximately 31 months or data cutoff date of 13 February 2015)

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: percentage of participants				
number (not applicable)	75.8	81.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival - PPS

End point title	Progression-Free Survival - PPS

End point description:

Progression-free survival was defined as the time between the day of randomization and the date of first documentation of disease progression or date of death, whichever occurred first, measured following RECIST Version 1.1 criteria. Disease progression was defined as a ≥20% increase in the sum of

diameters of target lesions, taking as reference the smallest sum on study including Baseline (nadir). In addition to the relative increase of 20%, the sum was also required to demonstrate an absolute increase of ≥5 mm. The 95% CI for median was computed using the method of Brookmeyer and Crowley. PPS population.

End point type	Secondary

End point timeframe:

From date of randomization until first occurrence of disease progression or death; assessed every 6 weeks (up to approximately 31 months or data cutoff date of 13 February 2015)

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: months				
median (confidence interval 95%)	5.388 (2.793 to 7.721)	4.37 (2.727 to 6.834)		

Statistical analyses

Statistical analysis title	Stratified Analysis

Statistical analysis description:

Stratified analysis included stratum of creatinine clearance (45 to 59 mL/min and ≥60 mL/min). Hazard ratio was estimated by Cox regression.

Comparison groups	Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg)
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6759
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.02

Statistical analysis title	Unstratified Analysis

Statistical analysis description:

Unstratified analysis. Hazard ratio was estimated by Cox regression.

Comparison groups	Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg)

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5764
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	2.05

Secondary: Percentage of Participants With Objective Response - PPS

End point title	Percentage of Participants With Objective Response - PPS

End point description:

Objective response was defined as the occurrence of either a complete response (CR) or partial response (PR) as determined by RECIST Version 1.1 based on investigator assessment. CR was defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) were required to have reduction in short axis to <10 mm. PR was defined as a ≥30% decrease in the sum of diameters of target lesions, taking as reference the Baseline sum diameters. The 95% CI was constructed using Blyth-Still-Casella method. PPS population.

End point type	Secondary

End point timeframe:

From date of randomization until first occurrence of disease progression or death; assessed every 6 weeks (up to approximately 31 months or data cutoff date of 13 February 2015)

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: percentage of participants				
number (confidence interval 95%)	57.6 (40.12 to 73.16)	50 (31.89 to 68.11)		

Statistical analyses

Statistical analysis title	Difference in Response Rates

Statistical analysis description:

The 95% CI for difference in response rates was constructed using the normal approximation to the binomial distribution.

Comparison groups	Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg)

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5402
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-7.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.75
upper limit	16.6

Statistical analysis title	Odds Ratio
Comparison groups	Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg)
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.96

Secondary: Trastuzumab Cmin on Day 21 of Cycles 1 to 11 - FAS

End point title	Trastuzumab Cmin on Day 21 of Cycles 1 to 11 - FAS

End point description:

Cmin samples were obtained in all participants randomized to receive Herceptin (FAS). The observed Cmin was recorded, averaged among all participants, and expressed in µg/mL. FAS population. Here, number of subjects analyzed reflects the number of participants who were evaluable for this endpoint. Here also, "n" reflects the number of participants who were evaluable for each category in the respective arms.

End point type	Secondary

End point timeframe:

Day 21 of Cycle 1, 2, 3, 4, 5, 7, 9, 11 (cycle length = 21 days)

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 1 (n=100,99)	17.1 (± 14.3)	18.1 (± 18.1)		
Cycle 2 (n=93,76)	19.2 (± 8.8)	35.3 (± 19.4)		
Cycle 3 (n=77,71)	23.2 (± 11.8)	40.7 (± 20.6)		
Cycle 4 (n=73,61)	25.9 (± 12.1)	47.6 (± 20.2)		
Cycle 5 (n=70,60)	26.7 (± 10.6)	49.3 (± 23.2)		
Cycle 7 (n=51,44)	31.4 (± 14.2)	58.1 (± 27.6)		
Cycle 9 (n=31,24)	33.7 (± 17.6)	61 (± 23.9)		
Cycle 11 (n=24,16)	32.5 (± 14.7)	68.4 (± 35.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trastuzumab Serum Concentration on Day 1 of Cycle 1 - FAS

End point title	Trastuzumab Serum Concentration on Day 1 of Cycle 1 - FAS

End point description:

Trastuzumab serum concentration samples were obtained in all participants randomized to receive Herceptin (FAS). The observed concentration values were recorded, averaged among all participants, and expressed in µg/mL. FAS population. Here, number of subjects analyzed reflects the number of participants who were evaluable for this endpoint. Here also, "n" reflects the number of participants who were evaluable for each category in the respective groups.

End point type	Secondary

End point timeframe:

Pre-dose (0 minutes) and within 15 minutes after end of 2-hour Herceptin infusion on Day 1 of Cycle 1 (cycle length = 21 days)

End point values	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	111		
Units: µg/mL				
arithmetic mean (standard deviation)				
Pre-dose (n=109,110)	0.168 (± 1.69)	0.0204 (± 0.123)		
End of infusion (n=110,111)	126 (± 59.6)	137 (± 55.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of randomization until 6 months after last dose of study drug or end of study (up to approximately 32 months or final data collection date of 25 August 2015)

Adverse event reporting additional description:

Safety evaluable population included all participants who were randomized and received at least one dose of any component of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Capecitabine + Cisplatin + Herceptin (6 mg/kg)

Reporting group description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg q3w as standard of care from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m^2 intravenously q3w plus capecitabine 800 mg/m^2 orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

Reporting group title	Capecitabine + Cisplatin + Herceptin (10 mg/kg)

Reporting group description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 10 mg/kg q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m^2 intravenously q3w plus capecitabine 800 mg/m^2 orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

Serious adverse events	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 147 (23.81%)	38 / 147 (25.85%)	
number of deaths (all causes)	77	84	
number of deaths resulting from adverse events			
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peripheral embolism			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
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			
Asthenia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 147 (0.68%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (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			
Infusion related reaction			

subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic duct injury			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 147 (0.68%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 147 (0.68%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			

subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 147 (4.76%)	6 / 147 (4.08%)	
occurrences causally related to treatment / all	0 / 8	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 147 (2.04%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			

subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 147 (0.00%)	4 / 147 (2.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	2 / 147 (1.36%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (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	2 / 147 (1.36%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	2 / 147 (1.36%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 147 (3.40%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	4 / 147 (2.72%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Renal failure			
subjects affected / exposed	3 / 147 (2.04%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective spondylitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenic sepsis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 147 (1.36%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sepsis			
subjects affected / exposed	2 / 147 (1.36%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tinea pedis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (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			
Decreased appetite			
subjects affected / exposed	2 / 147 (1.36%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 147 (0.68%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			

subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 147 (1.36%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 147 (0.68%)	
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	Capecitabine + Cisplatin + Herceptin (6 mg/kg)	Capecitabine + Cisplatin + Herceptin (10 mg/kg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 147 (83.67%)	122 / 147 (82.99%)	
Investigations			
Weight decreased			
subjects affected / exposed	10 / 147 (6.80%)	17 / 147 (11.56%)	
occurrences (all)	10	18	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 147 (5.44%)	2 / 147 (1.36%)	
occurrences (all)	11	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	47 / 147 (31.97%)	40 / 147 (27.21%)	
occurrences (all)	62	55	
Leukopenia			
subjects affected / exposed	26 / 147 (17.69%)	24 / 147 (16.33%)	
occurrences (all)	49	61	
Neutropenia			
subjects affected / exposed	61 / 147 (41.50%)	69 / 147 (46.94%)	
occurrences (all)	109	142	
Thrombocytopenia			
subjects affected / exposed	14 / 147 (9.52%)	14 / 147 (9.52%)	
occurrences (all)	19	18	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 147 (10.88%)	11 / 147 (7.48%)	
occurrences (all)	20	12	
Fatigue			
subjects affected / exposed	25 / 147 (17.01%)	23 / 147 (15.65%)	
occurrences (all)	33	30	
Oedema peripheral			
subjects affected / exposed	9 / 147 (6.12%)	6 / 147 (4.08%)	
occurrences (all)	10	8	
Pyrexia			

subjects affected / exposed	15 / 147 (10.20%)	14 / 147 (9.52%)	
occurrences (all)	19	19	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 147 (5.44%)	7 / 147 (4.76%)	
occurrences (all)	11	8	
Abdominal pain upper			
subjects affected / exposed	12 / 147 (8.16%)	11 / 147 (7.48%)	
occurrences (all)	13	12	
Constipation			
subjects affected / exposed	19 / 147 (12.93%)	25 / 147 (17.01%)	
occurrences (all)	24	35	
Diarrhoea			
subjects affected / exposed	24 / 147 (16.33%)	30 / 147 (20.41%)	
occurrences (all)	36	42	
Nausea			
subjects affected / exposed	55 / 147 (37.41%)	55 / 147 (37.41%)	
occurrences (all)	105	109	
Vomiting			
subjects affected / exposed	36 / 147 (24.49%)	42 / 147 (28.57%)	
occurrences (all)	71	83	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 147 (6.12%)	3 / 147 (2.04%)	
occurrences (all)	10	3	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	14 / 147 (9.52%)	20 / 147 (13.61%)	
occurrences (all)	14	23	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	7 / 147 (4.76%)	13 / 147 (8.84%)	
occurrences (all)	7	17	
Renal failure			
subjects affected / exposed	5 / 147 (3.40%)	8 / 147 (5.44%)	
occurrences (all)	7	8	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	32 / 147 (21.77%)	27 / 147 (18.37%)	
occurrences (all)	47	41	
Hypoalbuminaemia			
subjects affected / exposed	5 / 147 (3.40%)	10 / 147 (6.80%)	
occurrences (all)	8	14	
Hypocalcaemia			
subjects affected / exposed	9 / 147 (6.12%)	9 / 147 (6.12%)	
occurrences (all)	10	12	
Hypokalaemia			
subjects affected / exposed	6 / 147 (4.08%)	15 / 147 (10.20%)	
occurrences (all)	7	19	
Hyponatraemia			
subjects affected / exposed	3 / 147 (2.04%)	8 / 147 (5.44%)	
occurrences (all)	3	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2011	- Clarified the instructions for collection of pharmacokinetic samples for serial measurements of trastuzumab concentrations in case of dose delay of Herceptin. - Revised actions and maximum hold times for study drug administration for non-hematological Grade 3 and Grade 4 (excluding cardiac) and hematological toxicities (neutropenia) that were not specifically attributable to one component of study treatment but related to study treatment. - Clarified instructions for the reloading dose of Herceptin in case of delayed dose beyond 7 days for the higher dose Herceptin (8 mg/kg loading dose followed by 10 mg/kg q3w) and the standard of care dose Herceptin (8 mg/kg loading dose followed by 6 mg/kg q3w) treatment arms. - Provided revised guidance for dose modifications and timeframe of dose delay due to hematological toxicity attributable to capecitabine or cisplatin and revised platelet count threshold for assessment of need for dose modification or delay of capecitabine and/or cisplatin.
06 August 2013	- Provided clarification and updated instructions to Protocol B for the pharmacokinetic sampling schedule in case of delay of Herceptin administration. - The cardiac safety follow-up timeline was extended from 6 to 24 months. - An inclusion criterion (lung or liver plus at least one other organ in addition to the primary tumor must be involved by metastatic gastric tumor) was clarified by specifying the acceptability of metastases in other locations such as distant lymph node, peritoneum, and malignant pleural effusion as a second site of metastasis. - Updated exclusion criterion to add basal cell carcinoma of the skin within the last five years prior to enrollment was an allowed malignancy. Reporting instructions for abnormal liver function tests were included to address the identification/reporting of potential drug-induced liver injury (DILI). - Extracellular domain (ECD) analyses were included in Cycles 2 to 5 of the main study in order to ensure that a sufficient number of data were collected for the second pharmacokinetic interim analysis in order to fully understand the distribution of the shed ECD concentrations in participants with metastatic gastric cancer (MGC), and to enable an accurate assessment of whether the increase in HER2 ECD levels would have an impact on serum trastuzumab pharmacokinetics. These analyses were incorporated into the protocol to support the EMA issued Follow-Up Measure (FUM 70.1, 70.2, and 70.3) for the MGC filing in Europe (Type II Variation on EME/HC/000278/II/47).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Trial was stopped for futility based on pre-planned interim analysis results.

Notes: