Clinical trial results:
A Phase 2, Multicenter, Open-label Study of DS-8201a in Subjects with HER2-expressing Advanced Colorectal Cancer

Summary

EudraCT number	2017-003466-28
Trial protocol	GB ES IT
Global end of trial date	10 November 2020

Results information

Result version number	v2 (current)
This version publication date	18 August 2021
First version publication date	28 June 2021
Version creation reason	• New data added to full data set Report has been updated with final data.

Trial information

Trial identification

Sponsor protocol code	DS8201-A-J203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03384940
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC CTI: 173808

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo Inc.
Sponsor organisation address	211 Mt. Airy Rd., Basking Ridge, NJ, United States, 07920
Public contact	Global Clinical Director, Daiichi Sankyo Inc., +1 908992 6400, CTRinfo@dsi.com
Scientific contact	Global Clinical Director, Daiichi Sankyo Inc., +1 908992 6400, CTRinfo@dsi.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	10 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 August 2019
Global end of trial reached?	Yes
Global end of trial date	10 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the objective response rate (ORR) of DS-8201a in HER2-expressing advanced metastatic colorectal cancer patients

Protection of trial subjects:

The study protocol, amendments, the informed consent form(s) (ICF[s]), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). The study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Japan: 26
Country: Number of subjects enrolled	Italy: 41
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	86
EEA total number of subjects	45

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)	56
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 86 participants who met all inclusion criteria and no exclusion criteria were enrolled and treated at clinic centers in Japan, United States, Spain, and Italy.

Pre-assignment

Screening details:

After tissue screening, a total of 86 participants were eligible based on confirmation of HER2 status.

Period 1

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

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	DS-8201a Cohort A

Arm description:

Participants in Cohort A were HER2-positive (IHC 3+ or IHC 2+/ISH+) who received DS-8201a once every 3 weeks.

Arm type	Experimental
Investigational medicinal product name	DS-8201a
Investigational medicinal product code	
Other name	Trastuzumab deruxtecan
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

DS-8201a was administered as a sterile intravenous (IV) solution at a dose of the 6.4 mg/kg every 3 weeks (Q3W).

Arm title	DS-8201a Cohort B

Arm description:

Participants in Cohort B were HER2 IHC 2+/ISH - who received DS-8201a once every 3 weeks.

Arm type	Experimental
Investigational medicinal product name	DS-8201a
Investigational medicinal product code	
Other name	Trastuzumab deruxtecan
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

DS-8201a was administered as a sterile intravenous (IV) solution at a dose of the 6.4 mg/kg every 3 weeks (Q3W).

Arm title	DS-8201a Cohort C

Arm description:

Participants in Cohort C were HER2/IHC 1+ who received DS-8201a once every 3 weeks.

Arm type	Experimental

Investigational medicinal product name	DS-8201a
Investigational medicinal product code	
Other name	Trastuzumab deruxtecan
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

DS-8201a was administered as a sterile intravenous (IV) solution at a dose of the 6.4 mg/kg every 3 weeks (Q3W).

Number of subjects in period 1	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C
Started	53	15	18
Completed	0	0	0
Not completed	53	15	18
Clinical progression	4	-	3
Physician decision	1	1	-
Consent withdrawn by subject	3	1	-
Adverse event, non-fatal	7	1	1
Death	2	1	-
Not specified	-	-	1
Progressive disease	36	11	13

Baseline characteristics

Reporting groups	
Reporting group title	DS-8201a Cohort A
Reporting group description:	
Participants in Cohort A were HER2-positive (IHC 3+ or IHC 2+/ISH+) who received DS-8201a once every 3 weeks.	
Reporting group title	DS-8201a Cohort B
Reporting group description:	
Participants in Cohort B were HER2 IHC 2+/ISH - who received DS-8201a once every 3 weeks.	
Reporting group title	DS-8201a Cohort C
Reporting group description:	
Participants in Cohort C were HER2/IHC 1+ who received DS-8201a once every 3 weeks.	

Reporting group values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C
Number of subjects	53	15	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	35	8	13
From 65-84 years	18	7	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	57.5	61.5	58.5
standard deviation	± 11.72	± 11.95	± 9.97
Gender categorical Units: Subjects			
Female	28	5	7
Male	25	10	11

Reporting group values	Total		
Number of subjects	86		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	56		
From 65-84 years	30		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	40		
Male	46		

End points

End points reporting groups

Reporting group title	DS-8201a Cohort A
Reporting group description:	
Participants in Cohort A were HER2-positive (IHC 3+ or IHC 2+/ISH+) who received DS-8201a once every 3 weeks.	
Reporting group title	DS-8201a Cohort B
Reporting group description:	
Participants in Cohort B were HER2 IHC 2+/ISH - who received DS-8201a once every 3 weeks.	
Reporting group title	DS-8201a Cohort C
Reporting group description:	
Participants in Cohort C were HER2/IHC 1+ who received DS-8201a once every 3 weeks.	

Primary: Number of Participants With Best Objective Response Based on Independent Central Review (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Number of Participants With Best Objective Response Based on Independent Central Review (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer[1]

End point description:

Best objective response was reported based on independent central review. As per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, CR was defined as a disappearance of all target lesions, PR was defined as at least a 30% decrease in the sum of diameters of target lesions, and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD; at least a 20% increase in the sum of diameters of target lesions.

End point type	Primary

End point timeframe:

Baseline up to withdrawal of consent, progressive disease, or unacceptable toxicity (whichever occurs first), up to 18 months post-dose

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: Descriptive statistics were used to assess this outcome.

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Number of subjects				
number (not applicable)				
Confirmed CR	0	0	0	
Confirmed PR	24	0	0	
Confirmed SD	20	9	4	
Confirmed PD	5	5	10	
Confirmed Non-evaluable	4	1	4	
Unconfirmed CR	0	0	0	
Unconfirmed PR	26	0	0	
Unconfirmed SD	18	9	4	

Unconfirmed PD	5	5	10	
Unconfirmed Non-evaluable	4	1	4	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Objective Response Rate Based on Independent Central Review (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Number of Participants With Objective Response Rate Based on Independent Central Review (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer[2]

End point description:

Objective response rate (defined as CR+PR) was reported based on independent central review. As per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, CR was defined as a disappearance of all target lesions and PR was defined as at least a 30% decrease in the sum of diameters of target lesions.

End point type	Primary

End point timeframe:

Baseline up to withdrawal of consent, progressive disease, or unacceptable toxicity (whichever occurs first), up to 18 months post-dose

Notes:

[2] - 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: Descriptive statistics were used to assess this outcome.

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Number of subjects				
number (not applicable)				
Confirmed CR+PR	24	0	0	
Confirmed CR+PR (within 3 months)	10	0	0	
Confirmed CR+PR (within 6 months)	23	0	0	
Confirmed CR+PR (within 9 months)	24	0	0	
Confirmed CR+PR (within 12 months)	24	0	0	
Unconfirmed CR+PR	26	0	0	
Unconfirmed CR+PR (within 3 months)	20	0	0	
Unconfirmed CR+PR (within 6 months)	25	0	0	
Unconfirmed CR+PR (within 9 months)	25	0	0	
Unconfirmed CR+PR (within 12 months)	25	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Best Objective Response Based on Investigator (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Number of Participants With Best Objective Response Based on Investigator (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point description:

Best objective response was reported based on investigator. As per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, CR was defined as a disappearance of all target lesions, PR was defined as at least a 30% decrease in the sum of diameters of target lesions, and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD; at least a 20% increase in the sum of diameters of target lesions.

End point type	Secondary

End point timeframe:

Baseline up to withdrawal of consent, progressive disease, or unacceptable toxicity (whichever occurs first), up to 18 months post-dose

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Number of subjects				
number (not applicable)				
Confirmed CR	0	0	0	
Confirmed PR	25	0	0	
Confirmed SD	18	7	6	
Confirmed PD	6	7	8	
Confirmed Non-evaluable	4	1	4	
Unconfirmed CR	0	0	0	
Unconfirmed PR	28	0	0	
Unconfirmed SD	15	7	6	
Unconfirmed PD	6	7	8	
Unconfirmed Non-evaluable	4	1	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Objective Response Rate Based on Investigator (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Number of Participants With Objective Response Rate Based on Investigator (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point description:

Objective response rate (defined as CR+PR) was reported based on investigator. As per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, CR was defined as a disappearance of all target lesions and PR was defined as at least a 30% decrease in the sum of diameters of target lesions.

End point type	Secondary

End point timeframe:

Baseline up to withdrawal of consent, progressive disease, or unacceptable toxicity (whichever occurs first), up to 18 months post-dose

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Number of subjects				
number (not applicable)				
Confirmed CR+PR	25	0	0	
Unconfirmed CR+PR	28	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (Confirmed and Unconfirmed) Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Duration of Response (Confirmed and Unconfirmed) Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer[3]

End point description:

Duration of response (DoR) is defined as the time from the date of the first documentation of an objective response (CR[disappearance of all target lesions] or PR [at least a 30% decrease in the sum of diameters of target lesions]) to the date of the first documentation of PD (at least a 20% increase in the sum of diameters of target lesions). Duration of response was measured for responding participants (CR or PR) only. Month was calculated as (duration of response days × 12)/365.25 for duration of response and calculated as (time to response days × 12)/365.25 for time to response.

End point type	Secondary

End point timeframe:

Date of first documentation of objective response (CR or PR) up to date of first documentation of PD, up to approximately 18 months post-dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were used to assess this outcome.

End point values	DS-8201a Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Months				
median (confidence interval 95%)				
Confirmed DoR	7.0 (5.8 to 9.5)			
Unconfirmed DoR	7.0 (5.8 to 9.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Disease Control Rate (Confirmed and Unconfirmed) Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point description:

Disease control rate (DCR) was defined as the proportion of participants who achieved a best overall response of CR + PR + SD based on independent central review and investigator assessment. As per RECIST v1.1, CR was defined as a disappearance of all target lesions, PR was defined as at least a 30% decrease in the sum of diameters of target lesions, and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD; at least a 20% increase in the sum of diameters of target lesions).

End point type	Secondary

End point timeframe:

Baseline up to withdrawal of consent, progressive disease, or unacceptable toxicity (whichever occurs first), up to 18 months post-dose

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Number of subjects				
number (not applicable)				
Confirmed CR+PR+SD (Independent Central Review)	44	9	4	
Unconfirmed CR+PR+SD (Independent Central Review)	44	9	4	
Confirmed CR+PR+SD (Investigator)	43	7	6	
Unconfirmed CR+PR+SD (Investigator)	43	7	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Progression-Free Survival Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point description:

Progression-free survival (PFS) is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic progressive disease (PD) via independent radiologic facility review or death due to any cause. PD was defined as at least a 20% increase in the sum of diameters of target lesions.

End point type	Secondary

End point timeframe:

Date of first dose to date of first objective documentation of PD or death (whichever occurs first), up to approximately 18 months

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Months				
median (confidence interval 95%)				
Progression-free survival	6.9 (4.1 to 6.9)	2.1 (1.4 to 4.1)	1.4 (1.3 to 2.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival at Various Time Points Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Progression-Free Survival at Various Time Points Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point description:

Progression-free survival (PFS) is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic progressive disease (PD) via independent radiologic facility review or death due to any cause. PD was defined as at least a 20% increase in the sum of diameters of target lesions. Point estimates at 3, 6, 9, and 12 months are based on Kaplan-Meier estimate. CI is computed using the Brookmeyer-Crowley method. The point estimate percentage (95% confidence interval) at 3, 6, 9, and 12 months is being reported.

End point type	Secondary

End point timeframe:

Date of first dose to date of first objective documentation of PD or death (whichever occurs first), up to approximately 18 months

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Months				
median (confidence interval 95%)				
Progression-free survival at 3 months	74.4 (60.0 to 84.3)	38.3 (13.0 to 63.6)	7.5 (0.5 to 28.3)	
Progression-free survival at 6 months	55 (40.0 to 67.8)	0 (0 to 0)	0 (0 to 0)	
Progression-free survival at 9 months	34.1 (19.7 to 49.1)	0 (0 to 0)	0 (0 to 0)	
Progression-free survival at 12 months	19.0 (7.5 to 34.3)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Overall Survival Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point description:

Overall survival (OS) is defined as the time from the date of first dose to the date of death from any cause. There is no data for the upper confidence interval for Cohort B as not enough events occurred to estimate the confidence interval and it is denoted as 99.9 as N/A cannot be entered in this field.

End point type	Secondary

End point timeframe:

Time from the date of first dose to date of death from any cause, up to approximately 18 months

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Months				
median (confidence interval 95%)				
Overall survival	15.5 (8.8 to 20.8)	7.3 (3.0 to 99.9)	7.7 (2.2 to 13.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at Various Time Points Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point title	Overall Survival at Various Time Points Based on Independent Central Review Following DS-8201a Treatment in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Advanced Colorectal Cancer

End point description:

Overall survival (OS) is defined as the time from the date of first dose to the date of death from any cause. The point estimate percentage (95% confidence interval) at 3, 6, 9, and 12 months is being reported.

End point type	Secondary

End point timeframe:

Time from the date of first dose to date of death from any cause, up to approximately 18 months

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Months				
median (confidence interval 95%)				
Overall survival at 3 months	86.8 (74.3 to 93.5)	86.7 (56.4 to 96.5)	77.0 (49.7 to 90.7)	
Overall survival at 6 months	73.6 (59.5 to 83.4)	53.3 (26.3 to 74.4)	57.8 (31.0 to 77.3)	
Overall survival at 9 months	62.0 (47.5 to 73.5)	38.1 (14.6 to 61.6)	43.3 (18.9 to 65.7)	
Overall survival at 12 months	60.0 (45.5 to 71.8)	38.1 (14.6 to 61.6)	28.9 (9.3 to 52.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Maximum Serum Concentration (Cmax) Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point title	Pharmacokinetic Parameter Maximum Serum Concentration (Cmax) Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point description:

Maximum serum concentration (Cmax) of DS-8201a and total anti-HER2 antibody was assessed.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1, before infusion (BI), end of infusion (EOI); Day 8; Day 15; Cycle 2: Day 1, BI and EOI; Cycle 3: Day 1, BI, EOI, 4 hours after start of drug, and 7 hours after start of drug; Cycles 4 and 6: Day 1, BI and EOI

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: ug/mL				
arithmetic mean (standard deviation)				
DS-8201a	135 (± 32.7)	123 (± 29.5)	122 (± 41.5)	
Total anti-HER2 antibody	130 (± 35.1)	106 (± 24.6)	109 (± 35.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Maximum Serum Concentration (Cmax) of MAAA-11181a Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point title	Pharmacokinetic Parameter Maximum Serum Concentration (Cmax) of MAAA-11181a Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point description:

Maximum serum concentration (Cmax) of MAAA-1181a was assessed.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1, before infusion (BI), end of infusion (EOI); Day 8; Day 15; Cycle 2: Day 1, BI and EOI; Cycle 3: Day 1, BI, EOI, 4 hours after start of drug, and 7 hours after start of drug; Cycles 4 and 6: Day 1, BI and EOI

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: ng/mL				
arithmetic mean (standard deviation)				
MAAA-1181a	15.8 (± 7.67)	12.9 (± 6.40)	15.1 (± 5.30)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Time to Maximum Serum Concentration (Tmax) Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point title	Pharmacokinetic Parameter Time to Maximum Serum Concentration (Tmax) Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point description:

Time to maximum serum concentration (Tmax) of DS-8201a, total anti-HER2 antibody, and MAAA-1181a was assessed.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1, before infusion (BI), end of infusion (EOI); Day 8; Day 15; Cycle 2: Day 1, BI and EOI; Cycle 3: Day 1, BI, EOI, 4 hours after start of drug, and 7 hours after start of drug; Cycles 4 and 6: Day 1, BI and EOI

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: hours				
arithmetic mean (full range (min-max))				
DS-8201a (n=52, 6, 18)	1.95 (1.42 to 8.75)	1.72 (1.25 to 5.08)	3.00 (0.88 to 6.92)	
Total anti-HER2 antibody (n=52, 6, 18)	1.72 (1.42 to 6.95)	1.68 (1.25 to 7.08)	1.93 (0.88 to 6.92)	
MAAA-1181a (n=52, 6, 18)	5.17 (1.75 to 8.75)	5.00 (3.83 to 6.97)	5.25 (3.83 to 7.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Area Under the Concentration-time Curve (AUC) Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point title	Pharmacokinetic Parameter Area Under the Concentration-time Curve (AUC) Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point description:

Area under the concentration-time curve (AUC) from dosing until 21 days (AUC21d) and the last quantifiable concentration (AUClast) of DS-8201a and total anti-HER2 antibody were assessed.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1, before infusion (BI), end of infusion (EOI); Day 8; Day 15; Cycle 2: Day 1, BI and EOI; Cycle 3: Day 1, BI, EOI, 4 hours after start of drug, and 7 hours after start of drug; Cycles 4 and 6: Day 1, BI and EOI

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: ug*d/mL				
arithmetic mean (standard deviation)				
DS-8201a:AUC21d (n=51,13,16)	610 (± 198)	571 (± 208)	577 (± 219)	
DS-8201a:AUClast (n=53,15,18)	600 (± 204)	559 (± 211)	577 (± 237)	
Total anti-HER2 antibody:AUC21d (n=50,13,16)	661 (± 218)	569 (± 224)	574 (± 219)	
Total anti-HER2 antibody:AUClast (n=53,15,18)	638 (± 235)	558 (± 225)	555 (± 224)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Area Under the Concentration-time Curve (AUC) of MAAA-1181a Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point title	Pharmacokinetic Parameter Area Under the Concentration-time Curve (AUC) of MAAA-1181a Following Treatment With DS-8201a in Participants With HER2-expressing Advanced Colorectal Cancer

End point description:

Area under the concentration-time curve (AUC) from dosing until 21 days (AUC21d) and the last quantifiable concentration (AUClast) of MAAA-1181a were assessed.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1, before infusion (BI), end of infusion (EOI); Day 8; Day 15; Cycle 2: Day 1, BI and EOI; Cycle 3: Day 1, BI, EOI, 4 hours after start of drug, and 7 hours after start of drug; Cycles 4 and 6: Day 1, BI and EOI

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: ng*d/mL				
arithmetic mean (standard deviation)				
MAAA-1181a:AUC21d (n=45,12,11)	60.2 (± 42.7)	45.0 (± 28.1)	55.1 (± 19.6)	
MAAA-1181a:AUClast (n=53, 15, 18)	59.5 (± 42.1)	47.1 (± 29.4)	62.5 (± 19.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Emergent Adverse Events (TEAEs) Reported By ≥20% Of

Participants Following Treatment With DS-8201a in Subjects With HER2-expressing Advanced Colorectal Cancer

End point title	Treatment-Emergent Adverse Events (TEAEs) Reported By ≥20% Of Participants Following Treatment With DS-8201a in Subjects With HER2-expressing Advanced Colorectal Cancer

End point description:

A treatment-emergent adverse event (TEAE) is defined as any adverse event not present prior to the initiation of drug treatment or any adverse event already present that worsens in intensity or frequency following exposure to the drug treatment. TEAEs were graded using National Cancer Institute (NCI)-CTCAE version 4.03.

End point type	Secondary

End point timeframe:

From the date of signing the informed consent form up to 40 (+7) days after last dose, up to approximately 18 months

End point values	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	15	18	
Units: Number of subjects				
number (not applicable)				
Any TEAE	53	15	18	
Nausea	37	9	7	
Anaemia	21	4	6	
Decreased appetite	18	5	7	
Fatigue	21	7	3	
Neutrophil count decreased	20	2	4	
Platelet count decreased	17	4	7	
Vomiting	23	3	1	
Diarrhoea	19	0	4	
Alopecia	12	4	1	
Constipation	10	3	1	
Hypokalaemia	9	1	4	
Aspartate aminotransferase increased	6	1	4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the date of signing the informed consent form up to 40 (+7) days after last dose, up to approximately 18 months.

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) was defined as an AE that occurred, having been absent before the first dose of study drug, or having worsened in severity or seriousness after initiation of the study drug until 40 (+7) days after the last dose of the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	DS-8201a Cohort A

Reporting group description:

Participants in Cohort A were HER2-positive (IHC 3+ or IHC 2+/ISH+) who received DS-8201a once every 3 weeks.

Reporting group title	DS-8201a Cohort B

Reporting group description:

Participants in Cohort B were HER2/IHC 1+ who received DS-8201a once every 3 weeks.

Reporting group title	DS-8201a Cohort C

Reporting group description:

Participants in Cohort C were HER2 IHC 2+/ISH - who received DS-8201a once every 3 weeks.

Serious adverse events	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 53 (37.74%)	6 / 15 (40.00%)	12 / 18 (66.67%)
number of deaths (all causes)	36	10	12
number of deaths resulting from adverse events	2	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			

subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Meningism			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	2 / 53 (3.77%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Interstitial lung disease			
subjects affected / exposed	1 / 53 (1.89%)	2 / 15 (13.33%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected fistula			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia klebsiella			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 53 (5.66%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	DS-8201a Cohort A	DS-8201a Cohort B	DS-8201a Cohort C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 53 (100.00%)	15 / 15 (100.00%)	18 / 18 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 53 (5.66%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Hypotension			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Retinal vein occlusion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	6 / 53 (11.32%)	2 / 15 (13.33%)	3 / 18 (16.67%)
occurrences (all)	6	2	3
Disease progression			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	21 / 53 (39.62%)	7 / 15 (46.67%)	3 / 18 (16.67%)
occurrences (all)	21	7	3
Fluid retention			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
General physical health deterioration			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Generalised oedema			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	5 / 53 (9.43%)	0 / 15 (0.00%)	4 / 18 (22.22%)
occurrences (all)	5	0	4
Oedema			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	8 / 53 (15.09%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	8	1	1
Pyrexia			
subjects affected / exposed	8 / 53 (15.09%)	1 / 15 (6.67%)	3 / 18 (16.67%)
occurrences (all)	8	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 53 (15.09%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	8	2	0
Dyspnoea			

subjects affected / exposed	3 / 53 (5.66%)	3 / 15 (20.00%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
Interstitial lung disease			
subjects affected / exposed	4 / 53 (7.55%)	3 / 15 (20.00%)	1 / 18 (5.56%)
occurrences (all)	4	3	1
Productive cough			
subjects affected / exposed	3 / 53 (5.66%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 53 (3.77%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 53 (5.66%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	3	1	1
Mood altered			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 53 (9.43%)	1 / 15 (6.67%)	3 / 18 (16.67%)
occurrences (all)	5	1	3
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 53 (11.32%)	1 / 15 (6.67%)	4 / 18 (22.22%)
occurrences (all)	6	1	4
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	3	1	1
Blood bilirubin increased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 15 (6.67%)	2 / 18 (11.11%)
occurrences (all)	3	1	2
Blood calcium decreased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood creatinine increased			

subjects affected / exposed	5 / 53 (9.43%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	5	0	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	2	0	2
Blood magnesium decreased			
subjects affected / exposed	2 / 53 (3.77%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Blood potassium decreased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	3 / 53 (5.66%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Lymphocyte count decreased			
subjects affected / exposed	2 / 53 (3.77%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Neutrophil count decreased			
subjects affected / exposed	20 / 53 (37.74%)	2 / 15 (13.33%)	4 / 18 (22.22%)
occurrences (all)	20	2	4
Platelet count decreased			
subjects affected / exposed	17 / 53 (32.08%)	4 / 15 (26.67%)	7 / 18 (38.89%)
occurrences (all)	17	4	7
Weight decreased			
subjects affected / exposed	5 / 53 (9.43%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	5	0	1
White blood cell count decreased			
subjects affected / exposed	11 / 53 (20.75%)	1 / 15 (6.67%)	2 / 18 (11.11%)
occurrences (all)	11	1	2
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 53 (7.55%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	4	1	1
Headache			

subjects affected / exposed	2 / 53 (3.77%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Paraesthesia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Vasogenic cerebral oedema			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 53 (39.62%)	4 / 15 (26.67%)	6 / 18 (33.33%)
occurrences (all)	21	4	6
Leukocytosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	5 / 53 (9.43%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	5	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Eye disorders			
Dry eye			
subjects affected / exposed	5 / 53 (9.43%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
Eye pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Keratitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 53 (15.09%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	8	2	0
Abdominal pain upper			

subjects affected / exposed	3 / 53 (5.66%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Abdominal sepsis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Ascites			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	10 / 53 (18.87%)	3 / 15 (20.00%)	1 / 18 (5.56%)
occurrences (all)	10	3	1
Diarrhoea			
subjects affected / exposed	19 / 53 (35.85%)	0 / 15 (0.00%)	4 / 18 (22.22%)
occurrences (all)	19	0	4
Gastritis			
subjects affected / exposed	3 / 53 (5.66%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Ileus paralytic			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Intestinal obstruction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Intestinal prolapse			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	37 / 53 (69.81%)	9 / 15 (60.00%)	7 / 18 (38.89%)
occurrences (all)	37	9	7
Small intestinal obstruction			

subjects affected / exposed	1 / 53 (1.89%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Stomatitis			
subjects affected / exposed	6 / 53 (11.32%)	2 / 15 (13.33%)	1 / 18 (5.56%)
occurrences (all)	6	2	1
Vomiting			
subjects affected / exposed	23 / 53 (43.40%)	3 / 15 (20.00%)	1 / 18 (5.56%)
occurrences (all)	23	3	1
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cholecystitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 53 (22.64%)	4 / 15 (26.67%)	1 / 18 (5.56%)
occurrences (all)	12	4	1
Flushing			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Jaundice			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 53 (3.77%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Dysuria			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hydronephrosis			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Pollakiuria			

subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 53 (5.66%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Back pain			
subjects affected / exposed	5 / 53 (9.43%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 53 (3.77%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Myalgia			
subjects affected / exposed	3 / 53 (5.66%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Proctalgia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cancer pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	4 / 53 (7.55%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Fungal infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 53 (1.89%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Lung infection			
subjects affected / exposed	1 / 53 (1.89%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Oral candidiasis			

subjects affected / exposed	1 / 53 (1.89%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Oral herpes			
subjects affected / exposed	1 / 53 (1.89%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pneumonia			
subjects affected / exposed	1 / 53 (1.89%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pneumonia bacterial			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Sepsis			
subjects affected / exposed	3 / 53 (5.66%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Urinary tract infection			
subjects affected / exposed	5 / 53 (9.43%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	5	1	1
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Decreased appetite			
subjects affected / exposed	18 / 53 (33.96%)	5 / 15 (33.33%)	7 / 18 (38.89%)
occurrences (all)	18	5	7
Dehydration			
subjects affected / exposed	1 / 53 (1.89%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyperuricaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	2	0	2

Hypocalcaemia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Hypokalaemia			
subjects affected / exposed	9 / 53 (16.98%)	1 / 15 (6.67%)	4 / 18 (22.22%)
occurrences (all)	9	1	4
Hypomagnesaemia			
subjects affected / exposed	4 / 53 (7.55%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	4	1	1
Hyponatraemia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2017	Revised inclusion and exclusion criteria, adjustments made to dose modifications, managing adverse events, and to the description of prior/concomitant palliative radiotherapy, and modified screening criteria
25 January 2018	Updated risks and benefits for study subjects, clarified inclusion/exclusion criteria and conditions for troponin test, revised safety management and dose modification guidance for subjects, and clarified the safety profile for DS-8201a
05 July 2018	Clarified definitions relevant to Screening criteria and adverse event reporting, additional subgroup analysis for prior treatment with HER2 targeted regimen
26 April 2019	Clarified ILD biomarkers for analysis, revised ILD monitoring plan and dose modification language, and clarified reporting of ILD events
03 July 2020	Added exploring endpoint for COVID-19 infection, modified inclusion criteria and dose modification guidelines, updated list of prohibited medications and permitted therapies, updated blood sampling for COVID-19 and evaluations for ILD/pneumonitis, amended PK assessments, updated AE, SAE, and AESI reporting procedures

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported