Clinical trial results:
A Phase 2, Multicenter, Open-Label Study of DS-8201a, an Anti-HER2-Antibody Drug Conjugate (ADC) for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated With T-DM1.

Summary

EudraCT number	2016-004986-18
Trial protocol	ES BE GB FR IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	29 March 2020
First version publication date	29 March 2020

Trial information

Trial identification

Sponsor protocol code	DS8201-A-U201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03248492
WHO universal trial number (UTN)	-
Other trial identifiers	Project Moniker: DESTINY-Breast01

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Contact for Clinical Trial Information, Daiichi Sankyo Inc., 1 908-992-6400, CTRinfo@dsi.com
Scientific contact	Contact for Clinical Trial Information, Daiichi Sankyo Inc., 1 908-992-6400, 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	Interim
Date of interim/final analysis	21 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

•Objective response rate (ORR) per imaging assessment - Percentage of participants with objective response was assessed every six weeks from Cycle 1 Day 1 through disease progression, by independent central imaging facility review based on RECIST version 1.1

Protection of trial subjects:

The informed consent form was approved by the Ethics Committee or the Institutional Review Board. The study was conducted according to GCP and ethical principles that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2017
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: 29
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	United States: 77
Country: Number of subjects enrolled	Japan: 56
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	253
EEA total number of subjects	80

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)	189
From 65 to 84 years	61
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A total of 253 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomized to treatment (Part 1) or received DS-8201a at the recommended dose (Part 2).

Pre-assignment

Screening details:

In Part 1, subjects were randomized 1:1:1 to either 5.4 mg/kg, 6.4 mg/kg, or 7.4 mg/kg dose of DS-8201a. Two doses randomized 1:1 (6.4 mg/kg and 7.4 mg/kg) were further evaluated. In Part 2, all T-DM1 resistant refractory participants (Cohort 2a) or T-DM1 intolerant (Cohort 2b) received DS-8201a at the recommended dose.

Period 1

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

Blinding implementation details:

Part 1 of the study was randomized and consisted of the PK stage and Dose Finding stage. Part 2 was not randomized and all subjects received DS-8201a at the recommended dose determined in Part 1.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: DS-8201a Low Dose

Arm description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a low dose (5.4 mg/kg) in the
pharmacokinetic (PK) and dose-finding phases.

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

Dosage and administration details:

DS-8201a is sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) to be administered as low, medium and high intravenous (IV) doses for Part 1 of the trial. The dose for Part 2 will be determined based on results from Part 1.

Arm title	Part 1: DS-8201a Medium Dose

Arm description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a medium dose (6.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.

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

Dosage and administration details:

DS-8201a is sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) to be administered as low, medium and high intravenous (IV) doses for Part 1 of the trial. The dose for Part 2 will be determined based on results from Part 1.

Arm title	Part 1: DS-8201a High Dose

Arm description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a high dose (7.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.

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

Dosage and administration details:

DS-8201a is sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) to be administered as low, medium and high intravenous (IV) doses for Part 1 of the trial. The dose for Part 2 will be determined based on results from Part 1.

Arm title	Part 2a: DS-8201a Low Dose

Arm description:

All T-DM1 resistant/refractory (R/R) participants who were treated at the recommended (5.4 mg/kg) dose in Part 2a in the continuation phase.

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

Dosage and administration details:

DS-8201a is sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) to be administered as low, medium and high intravenous (IV) doses for Part 1 of the trial. The dose for Part 2 will be determined based on results from Part 1.

Arm title	Part 2b (Exploratory): DS-8201a Low Dose

Arm description:

All participants who were previously treated with T-DM1 and were randomized to receive DS8201a low dose (5.4 mg/kg) in Part 2b in the continuation phase.

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

Dosage and administration details:

DS-8201a is sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) to be administered as low, medium and high intravenous (IV) doses for Part 1 of the trial. The dose for Part 2 will be determined based on results from Part 1.

Number of subjects in period 1	Part 1: DS-8201a Low Dose	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose
Started	50	48	21
Completed	0	0	0
Not completed	50	48	21
Consent withdrawn by subject	3	3	-
Physician decision	1	-	1
Adverse event, non-fatal	6	6	8

Death	1	-	-
Not specified	-	1	-
Ongoing	23	26	3
Progressive disease per RECIST v1.1	16	12	9

Number of subjects in period 1	Part 2a: DS-8201a Low Dose	Part 2b (Exploratory): DS-8201a Low Dose
Started	130	4
Completed	0	0
Not completed	130	4
Consent withdrawn by subject	3	1
Physician decision	2	-
Adverse event, non-fatal	8	1
Death	6	-
Not specified	4	-
Ongoing	85	2
Progressive disease per RECIST v1.1	22	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: DS-8201a Low Dose
Reporting group description:	
T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a low dose (5.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.	
Reporting group title	Part 1: DS-8201a Medium Dose
Reporting group description:	
T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a medium dose (6.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.	
Reporting group title	Part 1: DS-8201a High Dose
Reporting group description:	
T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a high dose (7.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.	
Reporting group title	Part 2a: DS-8201a Low Dose
Reporting group description:	
All T-DM1 resistant/refractory (R/R) participants who were treated at the recommended (5.4 mg/kg) dose in Part 2a in the continuation phase.	
Reporting group title	Part 2b (Exploratory): DS-8201a Low Dose
Reporting group description:	
All participants who were previously treated with T-DM1 and were randomized to receive DS8201a low dose (5.4 mg/kg) in Part 2b in the continuation phase.	

Reporting group values	Part 1: DS-8201a Low Dose	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose
Number of subjects	50	48	21
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	33	16
From 65-84 years	14	15	5
85 years and over	1	0	0
Age continuous Units: years			
arithmetic mean	57.9	55.8	54.4
standard deviation	± 11.3	± 13.0	± 10.5
Gender categorical Units: Subjects			
Female	50	48	21
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	0

Asian	22	22	12
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	2	0	1
White	24	23	8
More than one race	1	1	0
Unknown or Not Reported	0	1	0
Region of Enrollment Units: Subjects			
South Korea	7	7	0
Belgium	0	2	0
United States	15	14	10
Japan	16	15	11
Italy	0	1	0
United Kingdom	0	0	0
France	2	1	0
Spain	10	8	0

Reporting group values	Part 2a: DS-8201a Low Dose	Part 2b (Exploratory): DS-8201a Low Dose	Total
Number of subjects	130	4	253
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)	101	4	189
From 65-84 years	27	0	61
85 years and over	2	0	3
Age continuous Units: years			
arithmetic mean	55.4	49.8	
standard deviation	± 11.9	± 9.2	-
Gender categorical Units: Subjects			
Female	130	4	253
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	2
Asian	47	1	104
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	1	1	5
White	76	1	132
More than one race	2	0	4
Unknown or Not Reported	4	0	5
Region of Enrollment			

Units: Subjects			
South Korea	25	1	40
Belgium	7	0	9
United States	36	2	77
Japan	14	0	56
Italy	8	1	10
United Kingdom	12	0	12
France	17	0	20
Spain	11	0	29

Subject analysis sets

Subject analysis set title	Part 1 and Part 2a: DS-8201a Low Dose
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All T-DM1 resistant/refractory (R/R) participants who were treated in Part 1 or Part 2a at the recommended (5.4 mg/kg) dose.

Subject analysis set title	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were previously treated with T-DM1 and were randomized to receive DS8201a low dose (5.4 mg/kg) in Part 1 or Part 2a or Part 2b.

Reporting group values	Part 1 and Part 2a: DS-8201a Low Dose	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose	
Number of subjects	180	184	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	136	140	
From 65-84 years	41	41	
85 years and over	3	3	
Age continuous Units: years			
arithmetic mean	56.1	56.0	
standard deviation	± 11.8	± 11.7	
Gender categorical Units: Subjects			
Female	180	184	
Male	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	69	70	
Native Hawaiian or Other Pacific Islander	1	1	

Black or African American	3	4	
White	100	101	
More than one race	3	3	
Unknown or Not Reported	4	4	
Region of Enrollment Units: Subjects			
South Korea	32	33	
Belgium	7	7	
United States	51	53	
Japan	30	30	
Italy	8	9	
United Kingdom	12	12	
France	19	19	
Spain	21	21	

End points

End points reporting groups

Reporting group title	Part 1: DS-8201a Low Dose

Reporting group description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a low dose (5.4 mg/kg) in the
pharmacokinetic (PK) and dose-finding phases.

Reporting group title	Part 1: DS-8201a Medium Dose

Reporting group description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a medium dose (6.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.

Reporting group title	Part 1: DS-8201a High Dose

Reporting group description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a high dose (7.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.

Reporting group title	Part 2a: DS-8201a Low Dose

Reporting group description:

All T-DM1 resistant/refractory (R/R) participants who were treated at the recommended (5.4 mg/kg) dose in Part 2a in the continuation phase.

Reporting group title	Part 2b (Exploratory): DS-8201a Low Dose

Reporting group description:

All participants who were previously treated with T-DM1 and were randomized to receive DS8201a low dose (5.4 mg/kg) in Part 2b in the continuation phase.

Subject analysis set title	Part 1 and Part 2a: DS-8201a Low Dose
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All T-DM1 resistant/refractory (R/R) participants who were treated in Part 1 or Part 2a at the recommended (5.4 mg/kg) dose.

Subject analysis set title	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were previously treated with T-DM1 and were randomized to receive DS8201a low dose (5.4 mg/kg) in Part 1 or Part 2a or Part 2b.

Primary: Objective Response Rate as Confirmed by Independent Central Review Following Intravenous Administration of 5.4 mg/kg DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)

End point title	Objective Response Rate as Confirmed by Independent Central Review Following Intravenous Administration of 5.4 mg/kg DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)[1]

End point description:

The number of participants with objective response was assessed every six weeks from Cycle 1 Day 1 through discontinuation of treatment, by independent central imaging facility review based on RECIST version 1.1.

End point type	Primary

End point timeframe:

At least 6 months after last participant enrolled received first dose up to 19 months (data cut off of 21 March 2019)

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 analyses were performed based on the study groups and the study drug administered for this outcome.

End point values	Part 1 and Part 2a: DS-8201a Low Dose	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	180	184		
Units: participants				
number (not applicable)	109	111		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate as Confirmed By the Investigator Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)

End point title	Objective Response Rate as Confirmed By the Investigator Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)[2]

End point description:

The number of participants with objective response is assessed every six weeks from Cycle 1 Day 1 through discontinuation of treatment. Investigator-assessed objective response rate (ORR) was defined as the proportion of participants who achieved a best overall response of complete response or partial response based on local radiologists/
investigators' tumor assessments.

End point type	Secondary

End point timeframe:

At least 6 months after last participant enrolled received first dose up to 19 months (data cut off of 21 March 2019)

Notes:

[2] - 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 analyses were performed based on the study groups and the study drug administered for this outcome.

End point values	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose	Part 1 and Part 2a: DS-8201a Low Dose	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	48	21	180	184
Units: participants				
number (not applicable)	37	18	116	118

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Tumor Response as Confirmed By the Investigator Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)

End point title	Best Overall Tumor Response as Confirmed By the Investigator Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)[3]

End point description:

Best overall tumor response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) by the investigator based on RECIST v1.1. Participants who were non-evaluable (NE) are also reported.

End point type	Secondary

End point timeframe:

At least 6 months after last participant enrolled received first dose up to 19 months (data cut off of 21 March 2019)

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 analyses were performed based on the study groups and the study drug administered for this outcome.

End point values	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose	Part 1 and Part 2a: DS-8201a Low Dose	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	48	21	180	184
Units: participants				
number (not applicable)				
Complete response	3	0	4	6
Partial response	34	18	112	112
Stable disease	10	3	59	61
Progressive disease	0	0	4	4
Non-evaluable	1	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate and Clinical Benefit Rate as Confirmed by Independent Central Review Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)

End point title	Disease Control Rate and Clinical Benefit Rate as Confirmed by Independent Central Review Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)[4]

End point description:

Number of participants with controlled disease and who received clinical benefit from treatment as assessed by independent central review. DCR was defined as the proportion of participants who achieved a best overall response of complete response, partial response, or stable disease. CBR was defined as the proportion of participants who achieved a best overall response of complete response or partial response or more than 6 months of stable disease.

End point type	Secondary

End point timeframe:

At least 6 months after last participant enrolled received first dose up to 19 months (data cut off of 21 March 2019)

Notes:

[4] - 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 analyses were performed based on the study groups and the study drug administered for this outcome.

End point values	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose	Part 1 and Part 2a: DS-8201a Low Dose	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	48	21	180	184
Units: participants				
number (not applicable)				
Disease control rate	47	21	175	179
Clinical benefit rate	41	20	127	130

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (Complete Response or Partial Response) as Confirmed by Independent Central Review Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)

End point title	Duration of Response (Complete Response or Partial Response) as Confirmed by Independent Central Review Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)[5]

End point description:

The estimated duration of confirmed response (complete response [CR] or partial response [PR]) was assessed by independent central review. Duration of response was defined as the time interval between the date of first documentation of objective response (CR or PR) and the date of the first objective documentation of disease progression or death due to any cause.

End point type	Secondary

End point timeframe:

At least 6 months after last participant enrolled received first dose up to 19 months (data cut off of 21 March 2019)

Notes:

[5] - 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 analyses were performed based on the study groups and the study drug administered for this outcome.

End point values	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose	Part 1 and Part 2a: DS-8201a Low Dose	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	33[6]	17[7]	109[8]	111[9]
Units: months				
number (confidence interval 95%)	8.3 (8.3 to 8.3)	6.0 (4.8 to 8.3)	0 (0 to 0)	0 (0 to 0)

Notes:

[6] - Participants with complete response (CR) or partial response (PR) were analyzed.

[7] - Participants with complete response (CR) or partial response (PR) were analyzed.

[8] - Participants with complete response (CR) or partial response (PR) were analyzed.

[9] - Participants with complete response (CR) or partial response (PR) were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival Estimate As Confirmed by Independent Central Review Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)

End point title	Progression-Free Survival Estimate As Confirmed by Independent Central Review Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)[10]

End point description:

The point estimate of progression-free survival (PFS) is reported. PFS was defined as the time interval between the date of randomization/registration and the first documentation of disease progression or death due to any cause.

End point type	Secondary

End point timeframe:

At least 6 months after last participant enrolled received first dose up to 19 months (data cut off of 21 March 2019)

Notes:

[10] - 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 analyses were performed based on the study groups and the study drug administered for this outcome.

End point values	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose	Part 1 and Part 2a: DS-8201a Low Dose	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	48	21	180	184
Units: months				
number (confidence interval 95%)	0 (0 to 0)	9.5 (7.4 to 13.2)	10.6 (10.6 to 10.6)	10.6 (10.6 to 10.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Sum of Diameters Over Time as Determined by Independent Central Review Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)

End point title	Percent Change From Baseline in Sum of Diameters Over Time as Determined by Independent Central Review Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Enrolled Analysis Set)[11]

End point description:

Best percent change in sum of diameters of measurable tumors was based on RECIST 1.1. The best percent change was defined as the percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Baseline up to Week 6, 12, 18, 24, 30, 36 post dose (as of data cut off of 21 March 2019)

Notes:

[11] - 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 analyses were performed based on the study groups and the study drug administered for this outcome.

End point values	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose	Part 1 and Part 2a: DS-8201a Low Dose	Part 1 + Part 2a + Part 2b: DS-8201a Low Dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	48	21	180	184
Units: percent change from baseline				
arithmetic mean (standard deviation)				
Baseline to Week 6 (n=43, 21, 164, 167)	-26.2 (± 18.3)	-32.9 (± 25.4)	-26.9 (± 21.6)	-26.9 (± 22.5)
Baseline to Week 12 (n=20, 21, 152, 154)	-39.6 (± 22.7)	-43.6 (± 28.1)	-39.9 (± 24.5)	-40.1 (± 24.9)
Baseline to Week 18 (n=37, 19, 136, 138)	-50.1 (± 22.1)	-58.5 (± 29.4)	-44.4 (± 27.8)	-44.9 (± 28.0)
Baseline to Week 24 (n=31, 17, 124, 125)	-56.3 (± 22.1)	-61.9 (± 32.0)	-49.2 (± 30.6)	-49.3 (± 30.5)
Baseline to Week 30 (n=30, 15, 80, 81)	-59.1 (± 26.1)	-63.9 (± 32.2)	-51.2 (± 29.2)	-51.5 (± 29.2)
Baseline to Week 36 (n=24, 9, 46, 46)	-61.0 (± 26.7)	-54.6 (± 32.2)	-55.5 (± 29.9)	-55.5 (± 29.9)
Best percent change from baseline(n=43,21,166,169)	-59.5 (± 28.2)	-65.3 (± 27.7)	-50.5 (± 28.3)	-50.6 (± 28.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Summary of Treatment-emergent Adverse Events (TEAEs) Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Safety Analysis Set)

End point title	Overall Summary of Treatment-emergent Adverse Events (TEAEs) Following Intravenous Administration of DS-8201a in Participants With Metastatic Breast Cancer (Safety Analysis Set)

End point description:

TEAEs were assessed by severity and seriousness according to unique criteria. Severity described the intensity of an event and was graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, where Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL); Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL; Grade 4: Life-threatening consequences; urgent intervention indicated; and Grade 5: Death related to AE. Serious TEAEs were defined as any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization, or causes prolongation of existing hospitalization.

End point type	Secondary

End point timeframe:

Day 0 to Day 47 post last dose (as of data cut off date of 21 March 2019)

End point values	Part 1: DS-8201a Low Dose	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose	Part 2a: DS-8201a Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	48	21	130
Units: participants				
number (not applicable)				
Any TEAE	50	48	21	129
Drug-related TEAEs	50	47	21	128
Drug-related TEAEs of CTCAE ≥Grade 3	26	32	16	48
Any serious TEAE	11	6	8	25
Drug-related serious TEAEs	6	4	5	10
TEAEs associated with drug discontinuation	6	6	8	8
Related TEAEs associated with drug discontinuation	6	6	8	7
TEAEs associated with dose reduction	13	19	11	21
Drug-related TEAEs associated with dose reduction	11	18	11	20
TEAEs associated with dose interruption	19	16	12	36
Related TEAEs associated with drug interruption	17	13	11	29
TEAEs associated with death	1	1	2	8
Drug-related TEAEs associated with death	0	0	1	2

End point values	Part 2b (Exploratory): DS-8201a Low Dose			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: participants				
number (not applicable)				
Any TEAE	4			
Drug-related TEAEs	4			
Drug-related TEAEs of CTCAE ≥Grade 3	3			
Any serious TEAE	0			
Drug-related serious TEAEs	0			
TEAEs associated with drug discontinuation	1			
Related TEAEs associated with drug discontinuation	1			
TEAEs associated with dose reduction	3			
Drug-related TEAEs associated with dose reduction	3			

TEAEs associated with dose interruption	2			
Related TEAEs associated with drug interruption	2			
TEAEs associated with death	0			
Drug-related TEAEs associated with death	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event (AE) data were collected from Day 0 through Day 47 post last dose of study drug (as of data cutoff date of 21 March 2019).

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiating the study drug until 47 days after last dose of the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Part 1: DS-8201a Low Dose

Reporting group description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a low dose (5.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.

Reporting group title	Part 1: DS-8201a Medium Dose

Reporting group description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a medium dose (6.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.

Reporting group title	Part 1: DS-8201a High Dose

Reporting group description:

T-DM1 resistant/refractory (R/R) participants randomized to receive DS-8201a high dose (7.4 mg/kg) in the pharmacokinetic (PK) and dose-finding phases.

Reporting group title	Part 2a: DS-8201a Low Dose

Reporting group description:

All T-DM1 resistant/refractory (R/R) participants who were treated at the recommended (5.4 mg/kg) dose in Part 2a in the continuation phase.

Reporting group title	Part 2b (Exploratory): DS-8201a Low Dose

Reporting group description:

All participants who were previously treated with T-DM1 and were randomized to receive DS8201a low dose (5.4 mg/kg) in Part 2b in the continuation phase.

Serious adverse events	Part 1: DS-8201a Low Dose	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 50 (22.00%)	6 / 48 (12.50%)	8 / 21 (38.10%)
number of deaths (all causes)	6	7	8
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 21 (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

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 21 (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
Disease progression			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (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
Reproductive system and breast disorders			
Genital hemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute respiratory failure			

subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 50 (4.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	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	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ilium fracture			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 21 (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
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (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
Presyncope			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (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			
Anemia			

subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (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
Febrile neutropenia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematuria			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock hemorrhagic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal abscess			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			

subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 50 (0.00%)	2 / 48 (4.17%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal hemorrhage			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (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
Vomiting			
subjects affected / exposed	2 / 50 (4.00%)	1 / 48 (2.08%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 21 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (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
Influenza			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (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
Parotitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 21 (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
Pneumonia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 21 (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
Sepsis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Hyperkalemia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalemia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2a: DS-8201a Low Dose	Part 2b (Exploratory): DS-8201a Low Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 130 (19.23%)	0 / 4 (0.00%)	
number of deaths (all causes)	13	0	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			

subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Genital hemorrhage			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Femoral neck fracture			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			

subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock hemorrhagic			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal abscess			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 130 (1.54%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 130 (2.31%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	3 / 130 (2.31%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal hemorrhage			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 130 (1.54%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Flank pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Osteomyelitis			

subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 130 (2.31%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 130 (1.54%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalemia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	2 / 130 (1.54%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1: DS-8201a Low Dose	Part 1: DS-8201a Medium Dose	Part 1: DS-8201a High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)	48 / 48 (100.00%)	21 / 21 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 50 (18.00%)	7 / 48 (14.58%)	0 / 21 (0.00%)
occurrences (all)	9	7	0
Fatigue			
subjects affected / exposed	21 / 50 (42.00%)	24 / 48 (50.00%)	11 / 21 (52.38%)
occurrences (all)	21	24	11
Malaise			
subjects affected / exposed	3 / 50 (6.00%)	3 / 48 (6.25%)	5 / 21 (23.81%)
occurrences (all)	3	3	5
Mucosal inflammation			
subjects affected / exposed	1 / 50 (2.00%)	2 / 48 (4.17%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Oedema peripheral			
subjects affected / exposed	2 / 50 (4.00%)	6 / 48 (12.50%)	0 / 21 (0.00%)
occurrences (all)	2	6	0
Pyrexia			
subjects affected / exposed	2 / 50 (4.00%)	10 / 48 (20.83%)	4 / 21 (19.05%)
occurrences (all)	2	10	4
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	9 / 50 (18.00%)	7 / 48 (14.58%)	4 / 21 (19.05%)
occurrences (all)	9	7	4
Dyspnoea			
subjects affected / exposed	5 / 50 (10.00%)	0 / 48 (0.00%)	2 / 21 (9.52%)
occurrences (all)	5	0	2
Epistaxis			
subjects affected / exposed	6 / 50 (12.00%)	3 / 48 (6.25%)	1 / 21 (4.76%)
occurrences (all)	6	3	1
Hypoxia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Interstitial lung disease			
subjects affected / exposed	4 / 50 (8.00%)	3 / 48 (6.25%)	5 / 21 (23.81%)
occurrences (all)	4	3	5
Pneumonitis			
subjects affected / exposed	4 / 50 (8.00%)	1 / 48 (2.08%)	2 / 21 (9.52%)
occurrences (all)	4	1	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 50 (6.00%)	2 / 48 (4.17%)	2 / 21 (9.52%)
occurrences (all)	3	2	2
Dizziness			
subjects affected / exposed	6 / 50 (12.00%)	4 / 48 (8.33%)	1 / 21 (4.76%)
occurrences (all)	6	4	1
Insomnia			
subjects affected / exposed	5 / 50 (10.00%)	5 / 48 (10.42%)	5 / 21 (23.81%)
occurrences (all)	5	5	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 50 (14.00%)	4 / 48 (8.33%)	7 / 21 (33.33%)
occurrences (all)	7	4	7
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 50 (18.00%)	5 / 48 (10.42%)	7 / 21 (33.33%)
occurrences (all)	9	5	7
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 50 (2.00%)	4 / 48 (8.33%)	6 / 21 (28.57%)
occurrences (all)	1	4	6
Blood bilirubin increased			
subjects affected / exposed	4 / 50 (8.00%)	3 / 48 (6.25%)	5 / 21 (23.81%)
occurrences (all)	4	3	5
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 50 (8.00%)	0 / 48 (0.00%)	3 / 21 (14.29%)
occurrences (all)	4	0	3
Ejection fraction decreased			
subjects affected / exposed	1 / 50 (2.00%)	1 / 48 (2.08%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 50 (10.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences (all)	5	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 50 (2.00%)	6 / 48 (12.50%)	1 / 21 (4.76%)
occurrences (all)	1	6	1
Lymphocyte count decreased			
subjects affected / exposed	3 / 50 (6.00%)	5 / 48 (10.42%)	2 / 21 (9.52%)
occurrences (all)	3	5	2
Neutrophil count decreased			
subjects affected / exposed	16 / 50 (32.00%)	17 / 48 (35.42%)	12 / 21 (57.14%)
occurrences (all)	16	17	12
Platelet count decreased			
subjects affected / exposed	8 / 50 (16.00%)	11 / 48 (22.92%)	7 / 21 (33.33%)
occurrences (all)	8	11	7
Troponin I increased			
subjects affected / exposed	3 / 50 (6.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Weight decreased			
subjects affected / exposed	5 / 50 (10.00%)	6 / 48 (12.50%)	4 / 21 (19.05%)
occurrences (all)	5	6	4
White blood cell count decreased			

subjects affected / exposed	12 / 50 (24.00%)	15 / 48 (31.25%)	13 / 21 (61.90%)
occurrences (all)	12	15	13
Hypokalemia			
subjects affected / exposed	3 / 50 (6.00%)	3 / 48 (6.25%)	4 / 21 (19.05%)
occurrences (all)	3	3	4
Injury, poisoning and procedural complications			
Infusion-related reaction			
subjects affected / exposed	3 / 50 (6.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	4 / 50 (8.00%)	5 / 48 (10.42%)	1 / 21 (4.76%)
occurrences (all)	4	5	1
Headache			
subjects affected / exposed	7 / 50 (14.00%)	10 / 48 (20.83%)	2 / 21 (9.52%)
occurrences (all)	7	10	2
Neuropathy peripheral			
subjects affected / exposed	2 / 50 (4.00%)	1 / 48 (2.08%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 50 (6.00%)	4 / 48 (8.33%)	2 / 21 (9.52%)
occurrences (all)	3	4	2
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	16 / 50 (32.00%)	20 / 48 (41.67%)	10 / 21 (47.62%)
occurrences (all)	16	20	10
Leukopenia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1

Lymphopenia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	7 / 50 (14.00%)	6 / 48 (12.50%)	5 / 21 (23.81%)
occurrences (all)	7	6	5
Thrombocytopenia			
subjects affected / exposed	2 / 50 (4.00%)	4 / 48 (8.33%)	2 / 21 (9.52%)
occurrences (all)	2	4	2
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	4 / 50 (8.00%)	5 / 48 (10.42%)	3 / 21 (14.29%)
occurrences (all)	4	5	3
Keratitis			
subjects affected / exposed	2 / 50 (4.00%)	3 / 48 (6.25%)	1 / 21 (4.76%)
occurrences (all)	2	3	1
Lacrimation increased			
subjects affected / exposed	0 / 50 (0.00%)	3 / 48 (6.25%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Visual impairment			
subjects affected / exposed	1 / 50 (2.00%)	2 / 48 (4.17%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Abdominal distension			
subjects affected / exposed	3 / 50 (6.00%)	1 / 48 (2.08%)	0 / 21 (0.00%)
occurrences (all)	3	1	0
Abdominal pain			
subjects affected / exposed	5 / 50 (10.00%)	2 / 48 (4.17%)	3 / 21 (14.29%)
occurrences (all)	5	2	3
Abdominal pain upper			

subjects affected / exposed	3 / 50 (6.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Ascites			
subjects affected / exposed	0 / 50 (0.00%)	3 / 48 (6.25%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Constipation			
subjects affected / exposed	16 / 50 (32.00%)	17 / 48 (35.42%)	10 / 21 (47.62%)
occurrences (all)	16	17	10
Diarrhea			
subjects affected / exposed	15 / 50 (30.00%)	13 / 48 (27.08%)	4 / 21 (19.05%)
occurrences (all)	15	13	4
Dyspepsia			
subjects affected / exposed	3 / 50 (6.00%)	5 / 48 (10.42%)	0 / 21 (0.00%)
occurrences (all)	3	5	0
Dysphagia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 50 (16.00%)	2 / 48 (4.17%)	2 / 21 (9.52%)
occurrences (all)	8	2	2
Haemorrhoids			
subjects affected / exposed	3 / 50 (6.00%)	2 / 48 (4.17%)	1 / 21 (4.76%)
occurrences (all)	3	2	1
Nausea			
subjects affected / exposed	38 / 50 (76.00%)	40 / 48 (83.33%)	13 / 21 (61.90%)
occurrences (all)	38	40	13
Stomatitis			
subjects affected / exposed	10 / 50 (20.00%)	13 / 48 (27.08%)	4 / 21 (19.05%)
occurrences (all)	10	13	4
Toothache			
subjects affected / exposed	3 / 50 (6.00%)	1 / 48 (2.08%)	0 / 21 (0.00%)
occurrences (all)	3	1	0
Vomiting			
subjects affected / exposed	23 / 50 (46.00%)	19 / 48 (39.58%)	7 / 21 (33.33%)
occurrences (all)	23	19	7
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	25 / 50 (50.00%)	28 / 48 (58.33%)	8 / 21 (38.10%)
occurrences (all)	25	28	8
Dry skin			
subjects affected / exposed	2 / 50 (4.00%)	1 / 48 (2.08%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Nail disorder			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 50 (0.00%)	3 / 48 (6.25%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Rash			
subjects affected / exposed	1 / 50 (2.00%)	6 / 48 (12.50%)	1 / 21 (4.76%)
occurrences (all)	1	6	1
Skin hyperpigmentation			
subjects affected / exposed	3 / 50 (6.00%)	0 / 48 (0.00%)	2 / 21 (9.52%)
occurrences (all)	3	0	2
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 50 (6.00%)	3 / 48 (6.25%)	1 / 21 (4.76%)
occurrences (all)	3	3	1
Back pain			
subjects affected / exposed	1 / 50 (2.00%)	2 / 48 (4.17%)	3 / 21 (14.29%)
occurrences (all)	1	2	31
Muscle spasms			
subjects affected / exposed	1 / 50 (2.00%)	1 / 48 (2.08%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Myalgia			
subjects affected / exposed	4 / 50 (8.00%)	3 / 48 (6.25%)	0 / 21 (0.00%)
occurrences (all)	4	3	0
Neck pain			

subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Pain in extremity			
subjects affected / exposed	2 / 50 (4.00%)	4 / 48 (8.33%)	2 / 21 (9.52%)
occurrences (all)	2	4	2
Infections and infestations			
Cellulitis			
subjects affected / exposed	3 / 50 (6.00%)	1 / 48 (2.08%)	0 / 21 (0.00%)
occurrences (all)	3	1	0
Conjunctivitis			
subjects affected / exposed	0 / 50 (0.00%)	3 / 48 (6.25%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Cystitis			
subjects affected / exposed	2 / 50 (4.00%)	2 / 48 (4.17%)	1 / 21 (4.76%)
occurrences (all)	2	2	1
Herpes zoster			
subjects affected / exposed	3 / 50 (6.00%)	0 / 48 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Influenza			
subjects affected / exposed	0 / 50 (0.00%)	2 / 48 (4.17%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Nasopharyngitis			
subjects affected / exposed	5 / 50 (10.00%)	3 / 48 (6.25%)	3 / 21 (14.29%)
occurrences (all)	5	3	3
Pharyngitis			
subjects affected / exposed	1 / 50 (2.00%)	3 / 48 (6.25%)	0 / 21 (0.00%)
occurrences (all)	1	3	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 50 (12.00%)	1 / 48 (2.08%)	1 / 21 (4.76%)
occurrences (all)	6	1	1
Urinary tract infection			
subjects affected / exposed	4 / 50 (8.00%)	3 / 48 (6.25%)	2 / 21 (9.52%)
occurrences (all)	4	3	2
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	15 / 50 (30.00%)	21 / 48 (43.75%)	6 / 21 (28.57%)
occurrences (all)	15	21	6
Hypoalbuminaemia			
subjects affected / exposed	1 / 50 (2.00%)	3 / 48 (6.25%)	4 / 21 (19.05%)
occurrences (all)	1	3	4
Hypomagnesemia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 48 (0.00%)	3 / 21 (14.29%)
occurrences (all)	2	0	3

Non-serious adverse events	Part 2a: DS-8201a Low Dose	Part 2b (Exploratory): DS-8201a Low Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 130 (99.23%)	4 / 4 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 130 (3.08%)	1 / 4 (25.00%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 130 (11.54%)	1 / 4 (25.00%)	
occurrences (all)	15	1	
Fatigue			
subjects affected / exposed	65 / 130 (50.00%)	2 / 4 (50.00%)	
occurrences (all)	65	2	
Malaise			
subjects affected / exposed	2 / 130 (1.54%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Mucosal inflammation			
subjects affected / exposed	10 / 130 (7.69%)	0 / 4 (0.00%)	
occurrences (all)	10	0	
Oedema peripheral			
subjects affected / exposed	8 / 130 (6.15%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Pyrexia			
subjects affected / exposed	11 / 130 (8.46%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	23 / 130 (17.69%)	0 / 4 (0.00%)	
occurrences (all)	23	0	
Dyspnoea			
subjects affected / exposed	19 / 130 (14.62%)	0 / 4 (0.00%)	
occurrences (all)	19	0	
Epistaxis			
subjects affected / exposed	16 / 130 (12.31%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
Hypoxia			
subjects affected / exposed	2 / 130 (1.54%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Interstitial lung disease			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			
subjects affected / exposed	5 / 130 (3.85%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 130 (5.38%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Dizziness			
subjects affected / exposed	9 / 130 (6.92%)	1 / 4 (25.00%)	
occurrences (all)	9	1	
Insomnia			
subjects affected / exposed	6 / 130 (4.62%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 130 (7.69%)	0 / 4 (0.00%)	
occurrences (all)	10	0	
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 130 (10.77%)	0 / 4 (0.00%)	
occurrences (all)	14	0	

Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 130 (5.38%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Blood bilirubin increased			
subjects affected / exposed	7 / 130 (5.38%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ejection fraction decreased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 130 (2.31%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 130 (3.08%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Lymphocyte count decreased			
subjects affected / exposed	11 / 130 (8.46%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Neutrophil count decreased			
subjects affected / exposed	21 / 130 (16.15%)	0 / 4 (0.00%)	
occurrences (all)	21	0	
Platelet count decreased			
subjects affected / exposed	16 / 130 (12.31%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
Troponin I increased			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	6 / 130 (4.62%)	1 / 4 (25.00%)	
occurrences (all)	6	1	
White blood cell count decreased			

subjects affected / exposed	20 / 130 (15.38%)	0 / 4 (0.00%)	
occurrences (all)	20	0	
Hypokalemia			
subjects affected / exposed	16 / 130 (12.31%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
Injury, poisoning and procedural complications			
Infusion-related reaction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	0 / 130 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 130 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	8 / 130 (6.15%)	1 / 4 (25.00%)	
occurrences (all)	8	1	
Headache			
subjects affected / exposed	26 / 130 (20.00%)	1 / 4 (25.00%)	
occurrences (all)	26	1	
Neuropathy peripheral			
subjects affected / exposed	7 / 130 (5.38%)	1 / 4 (25.00%)	
occurrences (all)	7	1	
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 130 (6.92%)	0 / 4 (0.00%)	
occurrences (all)	9	0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	31 / 130 (23.85%)	0 / 4 (0.00%)	
occurrences (all)	31	0	
Leukopenia			
subjects affected / exposed	3 / 130 (2.31%)	1 / 4 (25.00%)	
occurrences (all)	3	1	

Lymphopenia			
subjects affected / exposed	8 / 130 (6.15%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Neutropenia			
subjects affected / exposed	13 / 130 (10.00%)	1 / 4 (25.00%)	
occurrences (all)	13	1	
Thrombocytopenia			
subjects affected / exposed	5 / 130 (3.85%)	1 / 4 (25.00%)	
occurrences (all)	5	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	3 / 130 (2.31%)	1 / 4 (25.00%)	
occurrences (all)	3	1	
Eye disorders			
Dry eye			
subjects affected / exposed	16 / 130 (12.31%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
Keratitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	3 / 130 (2.31%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Visual impairment			
subjects affected / exposed	1 / 130 (0.77%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Abdominal distension			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	16 / 130 (12.31%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
Abdominal pain upper			

subjects affected / exposed	8 / 130 (6.15%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Ascites			
subjects affected / exposed	3 / 130 (2.31%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	46 / 130 (35.38%)	1 / 4 (25.00%)	
occurrences (all)	46	1	
Diarrhea			
subjects affected / exposed	33 / 130 (25.38%)	1 / 4 (25.00%)	
occurrences (all)	33	1	
Dyspepsia			
subjects affected / exposed	19 / 130 (14.62%)	0 / 4 (0.00%)	
occurrences (all)	19	0	
Dysphagia			
subjects affected / exposed	4 / 130 (3.08%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 130 (5.38%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Haemorrhoids			
subjects affected / exposed	5 / 130 (3.85%)	1 / 4 (25.00%)	
occurrences (all)	5	1	
Nausea			
subjects affected / exposed	101 / 130 (77.69%)	2 / 4 (50.00%)	
occurrences (all)	101	2	
Stomatitis			
subjects affected / exposed	11 / 130 (8.46%)	2 / 4 (50.00%)	
occurrences (all)	11	2	
Toothache			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	58 / 130 (44.62%)	2 / 4 (50.00%)	
occurrences (all)	58	2	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	61 / 130 (46.92%)	2 / 4 (50.00%)	
occurrences (all)	61	2	
Dry skin			
subjects affected / exposed	7 / 130 (5.38%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Nail disorder			
subjects affected / exposed	7 / 130 (5.38%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Pruritus			
subjects affected / exposed	4 / 130 (3.08%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Rash			
subjects affected / exposed	10 / 130 (7.69%)	0 / 4 (0.00%)	
occurrences (all)	10	0	
Skin hyperpigmentation			
subjects affected / exposed	4 / 130 (3.08%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 130 (0.77%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 130 (6.15%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Back pain			
subjects affected / exposed	14 / 130 (10.77%)	0 / 4 (0.00%)	
occurrences (all)	14	0	
Muscle spasms			
subjects affected / exposed	8 / 130 (6.15%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Myalgia			
subjects affected / exposed	7 / 130 (5.38%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Neck pain			

subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	3 / 130 (2.31%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Cystitis			
subjects affected / exposed	2 / 130 (1.54%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Herpes zoster			
subjects affected / exposed	1 / 130 (0.77%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	3 / 130 (2.31%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	8 / 130 (6.15%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Pharyngitis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	10 / 130 (7.69%)	0 / 4 (0.00%)	
occurrences (all)	10	0	
Urinary tract infection			
subjects affected / exposed	12 / 130 (9.23%)	1 / 4 (25.00%)	
occurrences (all)	12	1	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	37 / 130 (28.46%)	1 / 4 (25.00%)	
occurrences (all)	37	1	
Hypoalbuminaemia			
subjects affected / exposed	5 / 130 (3.85%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Hypomagnesemia			
subjects affected / exposed	4 / 130 (3.08%)	0 / 4 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2017	Revised study title, included additional endpoints, clarified randomization schedule and forms of the drug product, confirmed the analysis sets to be used, and updated information regarding dose modifications, adverse events of special interest, and study assessments.
22 January 2018	Updated phototoxicity study data, clarified patient enrollment procedures, updated inclusion and exclusion criteria, and revised dose modification guidance.
27 July 2018	Updated the starting dose of study drug in Part 2, included and/or revised dose modification criteria, clarified patient follow-up procedures, updated timing of relevant study assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported