# 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<br>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<br>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<br>Units: years | | | |
| arithmetic mean | 57.5 | 61.5 | 58.5 |
| standard deviation | ± 11.72 | ± 11.95 | ± 9.97 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 28 | 5 | 7 |
| Male | 25 | 10 | 11 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 86 | | |
| Age categorical<br>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