



Clinical trial results:

Open Label Phase 2 Study of Tisotumab Vedotin for Patients with Platinum-Resistant Ovarian Cancer with a Safety Run-in of a Dose-Dense Regimen

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2019-001219-22 |
| Trial protocol | ES IE BE DK IT |
| Global end of trial date | 08 February 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 13 February 2023 |
| First version publication date | 13 February 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | SGNTV-002 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03657043 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Seagen Inc. |
| Sponsor organisation address | 21823 30th Drive S.E., Bothell, United States, 98021 |
| Public contact | Chief Medical Officer, Seagen Inc., 1 8554732436, medinfo@seagen.com |
| Scientific contact | Chief Medical Officer, Seagen Inc., 1 8554732436, medinfo@seagen.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 | 02 November 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 February 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- (Safety run-in) Evaluate safety and tolerability of a dose-dense regimen of tisotumab vedotin • (Part A and B) Evaluate antitumor activity of tisotumab vedotin

Protection of trial subjects:

This study was conducted in accordance with applicable regulations/guidelines set forth by the Food and Drug Administration (FDA) in 21 CFR Parts 11, 50, 54, 56, and 312; the European Union (EU) Directive 2001/20/EC and 2005/28/EC; and with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Essential documents are retained in accordance with ICH GCP.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 21 March 2019 |
| 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 | United States: 57 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | Italy: 8 |
| Country: Number of subjects enrolled | Belgium: 6 |
| Country: Number of subjects enrolled | Ireland: 3 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Worldwide total number of subjects | 98 |
| EEA total number of subjects | 41 |

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) | 59 |
| From 65 to 84 years | 38 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

A total of 98 participants were enrolled into the Safety Run-In and Part B Expansion cohorts, of which 94 received study drug. No participants were enrolled into Part A. The date of first participant enrollment was 21-Mar-2019. The date of last participant completion was 08-Feb-2022.

Pre-assignment

Screening details:

Participants were screened for eligibility prior to enrollment.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | All Enrolled |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Safety Run-In 0.9 mg/kg 3Q4W |

Arm description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tisotumab vedotin |
| Investigational medicinal product code | |
| Other name | TIVDAK |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tisotumab vedotin 0.9 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

| | |
|------------------|------------------------------|
| Arm title | Safety Run-In 1.2 mg/kg 3Q4W |
|------------------|------------------------------|

Arm description:

Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tisotumab vedotin |
| Investigational medicinal product code | |
| Other name | TIVDAK |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tisotumab vedotin 1.2 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

| | |
|------------------|------------------|
| Arm title | Part B Expansion |
|------------------|------------------|

Arm description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|----------------------------------|
| Investigational medicinal product name | Tisotumab vedotin |
| Investigational medicinal product code | |
| Other name | TIVDAK |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tisotumab vedotin 0.9 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

| Number of subjects in period 1 | Safety Run-In 0.9 mg/kg 3Q4W | Safety Run-In 1.2 mg/kg 3Q4W | Part B Expansion |
|---|------------------------------|------------------------------|------------------|
| Started | 8 | 8 | 82 |
| Completed | 7 | 8 | 79 |
| Not completed | 1 | 0 | 3 |
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | - | - | 2 |
| Met exclusion criteria after enrollment | 1 | - | - |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | All Treated |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Safety Run-In 0.9 mg/kg 3Q4W |

Arm description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tisotumab vedotin |
| Investigational medicinal product code | |
| Other name | TIVDAK |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tisotumab vedotin 0.9 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

| | |
|------------------|------------------------------|
| Arm title | Safety Run-In 1.2 mg/kg 3Q4W |
|------------------|------------------------------|

Arm description:

Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|----------------------------------|
| Investigational medicinal product name | Tisotumab vedotin |
| Investigational medicinal product code | |
| Other name | TIVDAK |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tisotumab vedotin 1.2 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

| | |
|------------------|------------------|
| Arm title | Part B Expansion |
|------------------|------------------|

Arm description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tisotumab vedotin |
| Investigational medicinal product code | |
| Other name | TIVDAK |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tisotumab vedotin 0.9 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics are based on the All Treated population.

| Number of subjects in period 2 ^[2] | Safety Run-In 0.9 mg/kg 3Q4W | Safety Run-In 1.2 mg/kg 3Q4W | Part B Expansion |
|--|------------------------------|------------------------------|------------------|
| Started | 7 | 8 | 79 |
| Completed | 0 | 0 | 0 |
| Not completed | 7 | 8 | 79 |
| Consent withdrawn by subject | 1 | 1 | 3 |
| Study Closure by Sponsor | - | 2 | 17 |
| Death | 6 | 5 | 53 |
| Withdrawal - declined follow-up | - | - | 1 |
| Lost to follow-up | - | - | 4 |
| Withdrawal - subsequent treatment | - | - | 1 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 98 enrolled participants, 94 were treated and displayed here. Baseline characteristics are based on participants who received any amount of study drug.

Baseline characteristics

Reporting groups

| | |
|---|------------------------------|
| Reporting group title | Safety Run-In 0.9 mg/kg 3Q4W |
| Reporting group description: | |
| Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |
| Reporting group title | Safety Run-In 1.2 mg/kg 3Q4W |
| Reporting group description: | |
| Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |
| Reporting group title | Part B Expansion |
| Reporting group description: | |
| Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |

| Reporting group values | Safety Run-In 0.9 mg/kg 3Q4W | Safety Run-In 1.2 mg/kg 3Q4W | Part B Expansion |
|--|------------------------------|------------------------------|------------------|
| Number of subjects | 7 | 8 | 79 |
| Age categorical | | | |
| Units: Participants | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 64 years | 3 | 3 | 51 |
| >=65 years | 4 | 5 | 28 |
| Age Continuous | | | |
| Units: Years | | | |
| median | 69.0 | 67.5 | 60.0 |
| full range (min-max) | 50.0 to 87.0 | 51.0 to 74.0 | 38.0 to 81.0 |
| Sex/Gender, Customized | | | |
| Units: Participants | | | |
| Female | 7 | 8 | 79 |
| Intersex | 0 | 0 | 0 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Hispanic or Latino/a, or of Spanish Origin | 0 | 1 | 9 |
| Not of Hispanic or Latino/a, or of Spanish Origin | 6 | 7 | 69 |
| Unknown | 1 | 0 | 1 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 3 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 6 |
| White | 6 | 6 | 69 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 0 | 1 |
| Eastern Cooperative Oncology Group (ECOG) Performance Score | | | |
| Measure Description: 0=Normal activity; 1=Symptoms but ambulatory; 2=In bed <50% of the time; 3=In bed > 50% of the time; 4=100% bedridden; 5=Dead | | | |
| Units: Subjects | | | |

| | | | |
|---------|---|---|----|
| Grade 0 | 4 | 5 | 48 |
| Grade 1 | 3 | 3 | 31 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 94 | | |
| Age categorical Units: Participants | | | |
| <=18 years | 0 | | |
| Between 18 and 64 years | 57 | | |
| >=65 years | 37 | | |
| Age Continuous Units: Years | | | |
| median | | | |
| full range (min-max) | - | | |
| Sex/Gender, Customized Units: Participants | | | |
| Female | 94 | | |
| Intersex | 0 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino/a, or of Spanish Origin | 10 | | |
| Not of Hispanic or Latino/a, or of Spanish Origin | 82 | | |
| Unknown | 2 | | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 4 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 7 | | |
| White | 81 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 2 | | |
| Eastern Cooperative Oncology Group (ECOG) Performance Score | | | |
| Measure Description: 0=Normal activity; 1=Symptoms but ambulatory; 2=In bed <50% of the time; 3=In bed > 50% of the time; 4=100% bedridden; 5=Dead | | | |
| Units: Subjects | | | |
| Grade 0 | 57 | | |
| Grade 1 | 37 | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Safety Run-In 0.9 mg/kg 3Q4W |
| Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |
| Reporting group title | Safety Run-In 1.2 mg/kg 3Q4W |
| Reporting group description: Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |
| Reporting group title | Part B Expansion |
| Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |
| Reporting group title | Safety Run-In 0.9 mg/kg 3Q4W |
| Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |
| Reporting group title | Safety Run-In 1.2 mg/kg 3Q4W |
| Reporting group description: Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |
| Reporting group title | Part B Expansion |
| Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle | |
| Subject analysis set title | Part B Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set includes all participants who received any amount of study drug. | |
| Subject analysis set title | Part B Safety Analysis Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The Safety Analysis Set includes all participants who received any amount of study drug. | |
| Subject analysis set title | Part B PK Analysis Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: PK Analysis Set includes enrolled participants who received any amount of study drug and at least one PK parameter can be estimated. | |
| Subject analysis set title | Part B CA-125 Evaluable Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The CA-125 evaluable analysis set includes participants who have an elevated baseline CA-125 value of $\geq 2 \times$ ULN (upper limit of normal) within 2 weeks prior to the first dose of study drug. | |
| Subject analysis set title | Part B Full Analysis Set - Subjects with Confirmed CR or PR |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Subset of the Full Analysis Set includes all participants who received any amount of study drug and had a confirmed CR or PR. | |

Primary: Number of Participants with Dose-Limiting Toxicities (DLTs) (Safety Run-In Only)

| | |
|--|---|
| End point title | Number of Participants with Dose-Limiting Toxicities (DLTs) (Safety Run-In Only) ^[1] |
| End point description: Incidence of dose-limiting toxicity (DLT) was evaluated in participants enrolled in the Safety Run-In, who were followed for protocol-defined DLT events up to 28 days after the first dose of tisotumab | |

vedotin.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Up to 0.9 months | |

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: The planned analysis was to evaluate the incidence of DLTs, which was observed to occur in 1/8 participants, as reported here.

| | | | | |
|-----------------------------|------------------------------------|------------------------------------|--|--|
| End point values | Safety Run-In 0.9 mg/kg 3Q4W | Safety Run-In 1.2 mg/kg 3Q4W | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 8 | | |
| Units: Participants | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Confirmed Objective Response rate (ORR) (Part B)

| | |
|-----------------|---|
| End point title | Confirmed Objective Response rate (ORR) (Part B) ^[2] |
|-----------------|---|

End point description:

Proportion of participants who achieve a confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by the investigator

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 9.7 months

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: The ORR for Part B with 95% confidence interval provided for the end point is the statistical analysis.

| | | | | |
|-----------------------------------|-----------------------------|--|--|--|
| End point values | Part B Full Analysis Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 9.0 (3.6 to 17.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) (Part B)

| | |
|-----------------|---|
| End point title | Number of Participants with Adverse Events (AEs) (Part B) |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence in a patient or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Treatment emergent AEs (TEAEs) are defined as events that are new or worsened on or after receiving the first dose of study treatment and up through 30 days after the last dose of study treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 23.0 months

| End point values | Part B Safety Analysis Set | | | |
|---|----------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: Participants | | | | |
| Any TEAE | 79 | | | |
| Treatment-related TEAE | 67 | | | |
| Treatment-related Grade 3-4 TEAE | 14 | | | |
| Treatment-related Grade 5 TEAE | 0 | | | |
| Max severity of TEAE - Grade 1 | 7 | | | |
| Max severity of TEAE - Grade 2 | 35 | | | |
| Max severity of TEAE - Grade 3 | 32 | | | |
| Max severity of TEAE - Grade 4 | 3 | | | |
| Max severity of TEAE - Grade 5 | 2 | | | |
| Any treatment-emergent serious AE (SAE) | 28 | | | |
| Treatment-related SAE | 6 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed and unconfirmed ORR (Part B)

| | |
|-----------------|--|
| End point title | Confirmed and unconfirmed ORR (Part B) |
|-----------------|--|

End point description:

Proportion of participants who achieve a CR or PR according to RECIST v1.1 as assessed by the investigator

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 9.7 months

| End point values | Part B Expansion | Part B Full Analysis Set | | |
|-----------------------------------|---------------------|--------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 79 | 79 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 18.0 (10.0 to 27.9) | 18.0 (10.0 to 27.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cancer Antigen 125 (CA-125) response rate according to Gynecologic Cancer Intergroup (GCIG) criteria (Part B)

| | |
|------------------------|---|
| End point title | Cancer Antigen 125 (CA-125) response rate according to Gynecologic Cancer Intergroup (GCIG) criteria (Part B) |
| End point description: | Proportion of participants who have at least a 50% reduction in CA-125 value from baseline |
| End point type | Secondary |
| End point timeframe: | Up to 10.1 months |

| End point values | Part B CA-125 Evaluable Set | | | |
|-----------------------------------|-----------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 51 | | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 12.0 (4.4 to 23.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response according to the Gynecological Cancer Intergroup (GCIG) combined RECIST and CA-125 criteria (Part B)

| | |
|------------------------|--|
| End point title | Overall response according to the Gynecological Cancer Intergroup (GCIG) combined RECIST and CA-125 criteria (Part B) |
| End point description: | Proportion of participants whose best response is a CR or PR according to the GCIG combined RECIST and CA-125 criteria |
| End point type | Secondary |
| End point timeframe: | Up to 10.1 months |

| | | | | |
|-----------------------------------|--------------------------|--|--|--|
| End point values | Part B Full Analysis Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 11.0 (5.3 to 20.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) (Part B)

| | |
|---|-------------------------------------|
| End point title | Duration of response (DOR) (Part B) |
| End point description: Time from the first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD or death due to any cause, whichever comes first | |
| End point type | Secondary |
| End point timeframe: Up to 8.3 months | |

| | | | | |
|----------------------------------|---|--|--|--|
| End point values | Part B Full Analysis Set - Subjects with Confirmed CR or PR | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 7 ^[3] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.21 (3.02 to 999) | | | |

Notes:

[3] - 999 = Not Available

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) (Part B)

| | |
|--|-------------------------------------|
| End point title | Disease control rate (DCR) (Part B) |
| End point description: Proportion of participants who achieved a confirmed Complete Response(CR) or Partial Response (PR) per RECIST v1.1 as assessed by the investigator, or meet the Stable Disease (SD) criteria at least once after start of study treatment at a minimum interval of 12 weeks. | |
| End point type | Secondary |

End point timeframe:

Up to 3.0 months

| End point values | Part B Full Analysis Set | | | |
|-----------------------------------|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 54.4 (42.8 to 65.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) (Part B)

| | |
|---|---------------------------------|
| End point title | Time to response (TTR) (Part B) |
| End point description: Time from the start of study treatment to the first documentation of objective response (CR or PR that is subsequently confirmed) | |
| End point type | Secondary |
| End point timeframe: Up to 23.0 months | |

| End point values | Part B Full Analysis Set - Subjects with Confirmed CR or PR | | | |
|-------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 7 | | | |
| Units: Months | | | | |
| median (full range (min-max)) | 1.4 (1.0 to 3.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) (Part B)

| | |
|--|--|
| End point title | Progression-free survival (PFS) (Part B) |
| End point description: Time from the start of study treatment to the first documentation of PD or death due to any cause, whichever comes first | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 9.7 months | |

| | | | | |
|----------------------------------|--------------------------|--|--|--|
| End point values | Part B Full Analysis Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.73 (1.64 to 2.99) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) (Part B)

| | |
|--|--------------------------------|
| End point title | Overall survival (OS) (Part B) |
| End point description: | |
| Time from the start of study treatment to date of death due to any cause | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 23.0 months | |

| | | | | |
|----------------------------------|--------------------------|--|--|--|
| End point values | Part B Full Analysis Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 10.68 (7.75 to 12.81) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) parameter: Antibody-Drug Conjugate (ADC) Maximum concentration (Cmax) (Part B)

| | |
|---|---|
| End point title | Pharmacokinetic (PK) parameter: Antibody-Drug Conjugate (ADC) Maximum concentration (Cmax) (Part B) |
| End point description: | |
| ADC Cmax was derived from the PK blood samples collected. | |
| End point type | Secondary |

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 | 20.582 (± 26.963) | | | |
| Cycle 1, Dose 3 | 21.817 (± 26.823) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: ADC Time of Cmax (Tmax) (Part B)

| | |
|-----------------|--|
| End point title | PK parameter: ADC Time of Cmax (Tmax) (Part B) |
|-----------------|--|

End point description:

ADC Tmax was derived from the PK blood samples collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: Days | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 | 0.041 (± 53.112) | | | |
| Cycle 1, Dose 3 | 0.041 (± 78.407) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: ADC Area Under Concentration-Time Curve (AUC) (Part B)

| | |
|-----------------|--|
| End point title | PK parameter: ADC Area Under Concentration-Time Curve (AUC) (Part B) |
|-----------------|--|

End point description:

ADC AUC was derived from the PK blood samples collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: µg/mL*day | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 - AUC 7 Days-ADC | 25.198 (± 25.335) | | | |
| Cycle 1, Dose 3 - AUC 7 Days-ADC | 30.159 (± 32.261) | | | |
| Cycle 1, Dose 3 - AUC 14 Days-ADC | 31.716 (± 31.632) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Free Monomethyl Auristatin E (MMAE) Cmax (Part B)

| | |
|-----------------|---|
| End point title | PK parameter: Free Monomethyl Auristatin E (MMAE) Cmax (Part B) |
|-----------------|---|

End point description:

MMAE Cmax was derived from the PK blood samples collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 | 1.778 (\pm 66.636) | | | |
| Cycle 1, Dose 3 | 2.552 (\pm 52.442) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: MMAE Tmax (Part B)

| | |
|---|----------------------------------|
| End point title | PK parameter: MMAE Tmax (Part B) |
| End point description: MMAE Tmax was derived from the PK blood samples collected. | |
| End point type | Secondary |
| End point timeframe: Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle. | |

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: Days | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 | 2.061 (\pm 26.838) | | | |
| Cycle 1, Dose 3 | 2.101 (\pm 28.820) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: MMAE AUC (Part B)

| | |
|---|---------------------------------|
| End point title | PK parameter: MMAE AUC (Part B) |
| End point description: MMAE AUC was derived from the PK blood samples collected. | |
| End point type | Secondary |

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: ng/mL*day | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 - AUC Last-MMAE | 8.709 (\pm 63.747) | | | |
| Cycle 1, Dose 3 - AUC Last-MMAE | 16.578 (\pm 52.121) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: MMAE Trough Concentration (Ctough) (Part B)

| | |
|-----------------|---|
| End point title | PK parameter: MMAE Trough Concentration (Ctough) (Part B) |
|-----------------|---|

End point description:

MMAE Ctough was derived from the PK blood samples collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 3 | 0.230 (\pm 82.638) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Total Antibody (TAb) Cmax (Part B)

| | |
|-----------------|--|
| End point title | PK parameter: Total Antibody (TAb) Cmax (Part B) |
|-----------------|--|

End point description:

TAb Cmax was derived from the PK blood samples collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 | 18.418 (± 28.631) | | | |
| Cycle 1, Dose 3 | 19.955 (± 28.405) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: TAb Tmax (Part B)

| | |
|-----------------|---------------------------------|
| End point title | PK parameter: TAb Tmax (Part B) |
|-----------------|---------------------------------|

End point description:

TAb Tmax was derived from the PK blood samples collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: Days | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 | 0.041 (± 67.072) | | | |
| Cycle 1, Dose 3 | 0.043 (± 67.795) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: TAb Area Under Concentration-Time Curve (AUC) (Part B)

| | |
|-----------------|--|
| End point title | PK parameter: TAb Area Under Concentration-Time Curve (AUC) (Part B) |
|-----------------|--|

End point description:

TAbs AUC was derived from the PK blood samples collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

| End point values | Part B PK Analysis Set | | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 77 | | | |
| Units: µg/mL*day | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Dose 1 - AUC 7 Days-TAb | 35.535 (± 24.950) | | | |
| Cycle 1, Dose 3 - AUC 7 Days-TAb | 39.371 (± 29.218) | | | |
| Cycle 1, Dose 3 - AUC 14 Days-TAb | 42.240 (± 29.206) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of antitherapeutic antibodies (ATA) (Part B)

| | |
|-----------------|--|
| End point title | Incidence of antitherapeutic antibodies (ATA) (Part B) |
|-----------------|--|

End point description:

The proportion of participants who develop ATA at any time during the study. A positive baseline ATA result is considered positive post-baseline if the post-baseline ATA titer result is at least four times higher than the baseline result.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 6.9 months

| End point values | Part B Safety Analysis Set | | | |
|--|----------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 71 ^[4] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Baseline Negative - Negative post-baseline | 65 | | | |
| Baseline Negative - Positive post-baseline | 3 | | | |
| Baseline Positive - Negative post-baseline | 3 | | | |
| Baseline Positive - Positive post-baseline | 0 | | | |

Notes:

[4] - Participants in the Safety Analysis Set with a baseline and at least one post-baseline ATA sample.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious AEs were followed up to 10.5 months. Serious AEs and All-Cause Mortality were followed up to 31.6 months.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | PartBExpansion |
|-----------------------|----------------|

Reporting group description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| | |
|-----------------------|----------------------------|
| Reporting group title | SafetyRun-In(1.2mg/kg3Q4W) |
|-----------------------|----------------------------|

Reporting group description:

Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| | |
|-----------------------|----------------------------|
| Reporting group title | SafetyRun-In(0.9mg/kg3Q4W) |
|-----------------------|----------------------------|

Reporting group description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

| Serious adverse events | PartBExpansion | SafetyRun-In(1.2mg/kg3Q4W) | SafetyRun-In(0.9mg/kg3Q4W) |
|---|------------------|----------------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 28 / 79 (35.44%) | 4 / 8 (50.00%) | 2 / 7 (28.57%) |
| number of deaths (all causes) | 53 | 5 | 6 |
| number of deaths resulting from adverse events | 2 | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| General disorders and administration site conditions | | | |

| | | | |
|--|----------------|----------------|----------------|
| Fatigue alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| | 0 / 0 | 1 / 1 | 0 / 1 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| | 0 / 1 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Performance status decreased alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 0 / 79 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| | 0 / 0 | 0 / 0 | 0 / 1 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders Acute respiratory failure alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 2 / 79 (2.53%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| | 0 / 2 | 0 / 0 | 0 / 0 |
| | 0 / 1 | 0 / 0 | 0 / 0 |
| Pleural effusion alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 4 / 79 (5.06%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| | 0 / 4 | 0 / 0 | 0 / 1 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 2 / 79 (2.53%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| | 1 / 2 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (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 | | | |
| Angina pectoris | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Tachycardia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| alternative dictionary used: | | | |

| | | | | |
|---|----------------|----------------|----------------|--|
| MedDRA 25.0 | | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Ascites | | | | |
| alternative dictionary used: MedDRA 25.0 | | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Constipation | | | | |
| alternative dictionary used: MedDRA 25.0 | | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 3 / 8 (37.50%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Enteritis | | | | |
| alternative dictionary used: MedDRA 25.0 | | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 | |
| Intestinal obstruction | | | | |
| alternative dictionary used: MedDRA 25.0 | | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Nausea | | | | |
| alternative dictionary used: MedDRA 25.0 | | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | | |
| alternative dictionary used: MedDRA 25.0 | | | | |

| | | | |
|---|----------------|----------------|---------------|
| subjects affected / exposed | 3 / 79 (3.80%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Jaundice cholestatic | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Haematuria | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Urinary retention | | | |
| alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (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 |
| Urinary tract obstruction | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 pain | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Infections and infestations | | | |
| Cellulitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 | | | |
| alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Septic shock | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Urinary tract infection | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 0 / 7 (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 |

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

| Non-serious adverse events | PartBExpansion | SafetyRun-In(1.2mg/kg3Q4W) | SafetyRun-In(0.9mg/kg3Q4W) |
|---|------------------|----------------------------|----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 77 / 79 (97.47%) | 8 / 8 (100.00%) | 7 / 7 (100.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|--|------------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Asthenia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 19 / 79 (24.05%) 23 | 0 / 8 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Fatigue alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 25 / 79 (31.65%) 27 | 4 / 8 (50.00%) 4 | 2 / 7 (28.57%) 2 |
| Malaise alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 1 / 8 (12.50%) 2 | 0 / 7 (0.00%) 0 |
| Oedema peripheral alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 4 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Pyrexia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 5 | 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 6 | 0 / 8 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Vulvovaginal pain alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|------------------|----------------|----------------|
| Cough | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 7 | 0 | 1 |
| Dysphonia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 | 1 |
| Dyspnoea | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 9 / 79 (11.39%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Epistaxis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 36 / 79 (45.57%) | 3 / 8 (37.50%) | 4 / 7 (57.14%) |
| occurrences (all) | 46 | 4 | 4 |
| Hiccups | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasal congestion | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 9 / 79 (11.39%) | 3 / 8 (37.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 9 | 3 | 1 |
| Pharyngeal inflammation | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper-airway cough syndrome | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 8 (0.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 2 | 0 | 2 |
| Productive cough | | | |
| alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 |
| Psychiatric disorders Depression alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Insomnia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 1 / 8 (12.50%) 1 | 1 / 7 (14.29%) 1 |
| Investigations Alanine aminotransferase increased alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 5 | 0 / 8 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Aspartate aminotransferase increased alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 6 / 79 (7.59%) 6 | 0 / 8 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| International normalised ratio increased alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 7 | 0 / 8 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Weight decreased alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 5 | 1 / 8 (12.50%) 1 | 1 / 7 (14.29%) 1 |
| Injury, poisoning and procedural complications Corneal abrasion alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 2 |
| Incision site impaired healing | | | |

| | | | |
|--|------------------------|---------------------|---------------------|
| alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 |
| Nervous system disorders Cognitive disorder alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 |
| Dizziness alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 4 | 1 / 8 (12.50%) 1 | 1 / 7 (14.29%) 1 |
| Headache alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 5 | 0 / 8 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Paraesthesia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 |
| Peripheral sensory neuropathy alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 18 / 79 (22.78%) 20 | 2 / 8 (25.00%) 3 | 3 / 7 (42.86%) 3 |
| Restless legs syndrome alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 0 / 8 (0.00%) 0 | 2 / 7 (28.57%) 2 |
| Blood and lymphatic system disorders Anaemia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 23 / 79 (29.11%) 33 | 0 / 8 (0.00%) 0 | 4 / 7 (57.14%) 6 |
| Eye disorders | | | |

| | | | |
|---|------------------|----------------|----------------|
| Blepharitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 9 | 0 | 1 |
| Cataract nuclear | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Conjunctival haemorrhage | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| Conjunctival ulcer | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Conjunctivitis allergic | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dacryostenosis acquired | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry eye | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 12 / 79 (15.19%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 14 | 1 | 0 |
| Ectropion | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Entropion | | | |
| alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 0 | 1 |
| Eye discharge | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Eye pain | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Keratitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Lacrimation increased | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Punctate keratitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 2 / 8 (25.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Symblepharon | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Vision blurred | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 9 / 79 (11.39%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 10 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 8 / 79 (10.13%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 9 | 1 | 0 |
| Abdominal pain | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 22 / 79 (27.85%) | 3 / 8 (37.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 27 | 3 | 0 |
| Abdominal pain upper | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 7 | 1 | 2 |
| Constipation | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 17 / 79 (21.52%) | 3 / 8 (37.50%) | 2 / 7 (28.57%) |
| occurrences (all) | 20 | 4 | 2 |
| Diarrhoea | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 18 / 79 (22.78%) | 2 / 8 (25.00%) | 4 / 7 (57.14%) |
| occurrences (all) | 25 | 2 | 4 |
| Gastrooesophageal reflux disease | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 3 | 1 | 1 |
| Nausea | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 30 / 79 (37.97%) | 2 / 8 (25.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 37 | 2 | 2 |
| Stomatitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 0 | 1 |
| Vomiting | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 15 / 79 (18.99%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 19 | 1 | 2 |

| | | | |
|---|------------------|----------------|----------------|
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 16 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 10 / 79 (12.66%) | 2 / 8 (25.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 10 | 2 | 1 |
| Dermatitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis contact | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry skin | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Rash erythematous | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Urticaria | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rash maculo-papular | | | |

| | | | |
|---|---|---|--|
| alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Renal and urinary disorders Acute kidney injury alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) Dysuria alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) Haematuria alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 1 / 79 (1.27%) 1 4 / 79 (5.06%) 6 | 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 |
| Endocrine disorders Inappropriate antidiuretic hormone secretion alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) Back pain alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) Limb discomfort alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 7 / 79 (8.86%) 7 7 / 79 (8.86%) 7 0 / 79 (0.00%) 0 | 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 |

| | | | |
|---|------------------------|---------------------|---------------------|
| Muscle spasms alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Musculoskeletal chest pain alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Myalgia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 8 / 79 (10.13%) 9 | 0 / 8 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Pain in extremity alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 5 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Infections and infestations Acute sinusitis alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Conjunctivitis alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 25 / 79 (31.65%) 33 | 1 / 8 (12.50%) 1 | 2 / 7 (28.57%) 3 |
| Conjunctivitis viral alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 1 |
| Device related infection alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 7 (0.00%) 0 |
| Gingivitis alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Pneumonia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pustule | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinusitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 2 / 8 (25.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 6 | 2 | 2 |
| Tooth infection | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary tract infection | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 5 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 25 / 79 (31.65%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 29 | 1 | 1 |
| Hyperglycaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Dehydration | | | |
| alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 8 / 79 (10.13%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 8 | 1 | 0 |
| Hypoalbuminaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Hyperuricaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Hypocalcaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Hypokalaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 14 / 79 (17.72%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 17 | 0 | 2 |
| Hypomagnesaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 10 / 79 (12.66%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 13 | 0 | 1 |
| Hyponatraemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 12 October 2018 | Removed required on-treatment ophthalmological exam. Updated exclusion criteria from "peripheral neuropathy > Grade 1" to "peripheral neuropathy ≥ Grade 2." Changes to required ocular premedication and preventive eye therapy. Additional administrative changes and clarifications. |
| 02 May 2019 | Revised bevacizumab exposure criteria for safety run-in participants. Revise eGFR inclusion criteria. Remove 3 month PFS and 12 month OS timepoints. Additional corrections, administrative changes, and clarifications. |
| 17 October 2019 | Part B cohort added and number of planned participants updated to reflect added participants in Part B. 1.2 mg/kg dose escalation added to safety run-in. Additional corrections, administrative changes, and clarifications. |
| 24 August 2020 | Changed Part B to enroll approximately 80 participants. Updated exclusion criteria to permit anticoagulation and antiplatelet therapies. Updated inclusion criteria for prior treatments. Addition of interim analysis. Additional administrative changes and clarifications. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported