# Clinical trial results:
# A Phase 2, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of GS-5745 Combined with Nivolumab versus Nivolumab Alone in Subjects with Unresectable or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma

## Summary

| | |
|---|---|
| EudraCT number | 2016-001402-41 |
| Trial protocol | DE HU GB BE ES IT |
| Global end of trial date | 23 August 2019 |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 03 September 2020 |
| First version publication date | 03 September 2020 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | GS-US-296-2013 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02864381 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com |
| Scientific contact | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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 | 23 August 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 November 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 August 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate and compare the efficacy of andecaliximab (GS-5745) in combination with nivolumab versus nivolumab alone in adults with recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 September 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 35 |
| Country: Number of subjects enrolled | United States: 28 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Poland: 14 |
| Country: Number of subjects enrolled | Spain: 14 |
| Country: Number of subjects enrolled | Italy: 13 |
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | Hungary: 3 |
| Worldwide total number of subjects | 144 |
| EEA total number of subjects | 109 |

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) | 90 |
| From 65 to 84 years | 54 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at study sites in Australia, Europe, and the United States. The first participant was screened on 01 September 2016. The last study visit occurred on 23 August 2019.

### Pre-assignment

Screening details:

187 participants were screened.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Andecaliximab + Nivolumab |

Arm description:

Andecaliximab 800 mg administered via intravenous (IV) infusion plus nivolumab 3 mg/kg administered via IV infusion every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent (up to 34 weeks at the time of the primary efficacy analysis; up to 101 weeks at the time of the safety follow-up analysis).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Andecaliximab |
| Investigational medicinal product code | |
| Other name | GS-5745 |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

800 mg administered via IV infusion every 2 weeks

| | |
|---|---|
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 mg/kg administered via IV infusion every 2 weeks

| | |
|---|---|
| **Arm title** | Nivolumab |

Arm description:

Nivolumab 3 mg/kg administered via IV infusion every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent (up to 41 weeks at the time of the primary efficacy analysis; up to 97 weeks at the time of the safety follow-up analysis).

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 mg/kg administered via IV infusion every 2 weeks

| **Number of subjects in period 1** | Andecaliximab + Nivolumab | Nivolumab |
|---|---|---|
| Started | 72 | 72 |
| Completed | 0 | 0 |
| Not completed | 72 | 72 |
| Withdrew Consent | 5 | 6 |
| Reason Unknown | 7 | 3 |
| Death | 58 | 61 |
| Investigator's Discretion | 1 | - |
| Protocol Violation | - | 1 |
| Lost to follow-up | 1 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Andecaliximab + Nivolumab |
| Reporting group description: | |
| Andecaliximab 800 mg administered via intravenous (IV) infusion plus nivolumab 3 mg/kg administered via IV infusion every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent (up to 34 weeks at the time of the primary efficacy analysis; up to 101 weeks at the time of the safety follow-up analysis). | |
| Reporting group title | Nivolumab |
| Reporting group description: | |
| Nivolumab 3 mg/kg administered via IV infusion every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent (up to 41 weeks at the time of the primary efficacy analysis; up to 97 weeks at the time of the safety follow-up analysis). | |

| Reporting group values | Andecaliximab + Nivolumab | Nivolumab | Total |
|---|---|---|---|
| Number of subjects | 72 | 72 | 144 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 58 | 59 | |
| standard deviation | ± 12.1 | ± 11.8 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | 22 | 45 |
| Male | 49 | 50 | 99 |
| Race | | | |
| Not Permitted=local regulators did not allow collection of race information. | | | |
| Units: Subjects | | | |
| Asian | 1 | 1 | 2 |
| Black | 2 | 0 | 2 |
| White | 55 | 61 | 116 |
| Not Permitted | 12 | 8 | 20 |
| Other | 2 | 2 | 4 |
| Ethnicity | | | |
| Not Permitted=local regulators did not allow collection of ethnicity information. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 3 | 5 |
| Not Hispanic or Latino | 59 | 61 | 120 |
| Not Permitted | 11 | 8 | 19 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Andecaliximab + Nivolumab |

Reporting group description:

Andecaliximab 800 mg administered via intravenous (IV) infusion plus nivolumab 3 mg/kg administered via IV infusion every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent (up to 34 weeks at the time of the primary efficacy analysis; up to 101 weeks at the time of the safety follow-up analysis).

| | |
|---|---|
| Reporting group title | Nivolumab |

Reporting group description:

Nivolumab 3 mg/kg administered via IV infusion every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent (up to 41 weeks at the time of the primary efficacy analysis; up to 97 weeks at the time of the safety follow-up analysis).

### Primary: Objective Response Rate (ORR)

| | |
|---|---|
| End point title | Objective Response Rate (ORR) |

End point description:

ORR was defined as the percentage of participants with confirmed overall best response of complete response (CR) or partial response (PR) after starting study drug but before starting any new chemotherapy or radiotherapy as assessed by the investigator according to Response Criteria in Solid Tumors (RECIST) version 1.1. CR was defined as the disappearance of all target lesions and disappearance of all non-target lesions and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The Intent-to-treat Analysis Set included all participants who were randomized in the study.

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

End point timeframe:

Start of treatment to the time when the last participant is treated for 6 months or discontinued, whichever is earlier

| **End point values** | Andecaliximab + Nivolumab | Nivolumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 72 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 9.7 (4.0 to 19.0) | 6.9 (2.3 to 15.5) | | |

### Statistical analyses

| **Statistical analysis title** | Andecaliximab+Nivolumab vs Nivolumab |
|---|---|
| Comparison groups | Andecaliximab + Nivolumab v Nivolumab |

| | |
|---|---|
| Number of subjects included in analysis | 144 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8 [1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 6.1 |

Notes:

[1] - P-value is derived from Cochran-Mantel-Haenszel (CMH) test stratified by programmed death ligand 1 (PD-L1) stratification factor status. Odds ratio is derived from CMH test stratified by PD-L1 stratus, the Nivolumab alone arm serves as the reference.

## Secondary: Progression Free Survival (PFS)

| | |
|---|---|
| End point title | Progression Free Survival (PFS) |

End point description:

PFS was defined as the interval in months from the date of randomization to the earlier of the first documentation of definitive disease progression or death from any cause. The first definitive progressive disease (PD) was defined as the first radiation therapy, the first clinical PD, and the first confirmed imaging PD, whichever came first. Participants without PD or death and participants with PD after starting new anti-cancer therapy are censored at the last tumor assessment date. Participants in the Intent-to-treat Analysis Set were analyzed.

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

End point timeframe:

Andecaliximab + Nivolumab median follow-up time: 7.0 months; Nivolumab median follow-up time: 7.1 months

| End point values | Andecaliximab + Nivolumab | Nivolumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 72 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.840 (1.807 to 2.004) | 1.856 (1.741 to 1.906) | | |

## Statistical analyses

| Statistical analysis title | Andecaliximab+Nivolumab vs Nivolumab |
|---|---|
| Comparison groups | Andecaliximab + Nivolumab v Nivolumab |
| Number of subjects included in analysis | 144 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.306 [2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.836 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.589 |
| upper limit | 1.189 |

Notes:

[2] - P-value is derived from log-rank test stratified by PD-L1 stratification factor status. Hazard ratio is derived from Cox model stratified by PD-L1 stratification factor status, the Nivolumab alone arm serves as the reference.

## Secondary: Overall Survival (OS)

| | |
|---|---|
| End point title | Overall Survival (OS) |

End point description:

OS was defined as the interval from the date of randomization to death from any cause. 99999=not applicable (NA). Upper 95% Confidence Interval (CI) were not estimable due to the low number of participants with events. Surviving participants are censored at the last date known alive. Participants in the Intent-to-treat Analysis Set were analyzed.

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

End point timeframe:

Andecaliximab + Nivolumab median follow-up time: 7.0 months; Nivolumab median follow-up time: 7.0 months

| **End point values** | Andecaliximab + Nivolumab | Nivolumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 72 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.162 (4.797 to 99999) | 5.881 (3.483 to 10.908) | | |

### Statistical analyses

| **Statistical analysis title** | Andecaliximab+Nivolumab vs Nivolumab |
|---|---|
| Comparison groups | Andecaliximab + Nivolumab v Nivolumab |
| Number of subjects included in analysis | 144 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.312 [3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.786 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.491 |
| upper limit | 1.257 |

Notes:

[3] - P-value is derived from log-rank test stratified by PD-L1 stratification factor status. Hazard ratio is derived from Cox model stratified by PD-L1 stratification factor status, the Nivolumab alone arm serves as the reference.

## Secondary: Duration of Response (DOR)

| End point title | Duration of Response (DOR) |
|---|---|

End point description:

DOR was defined as the interval from the date of the first response (complete or partial response) was achieved to the earlier of the first documentation of definitive disease progression or death from any cause. 99999=NA. Median and Upper 95% CI were not estimable due to the low number of participants with events. Participants in the Intent-to-treat Analysis Set who achieved CR or PR were analyzed.

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

End point timeframe:

Andecaliximab + Nivolumab median follow-up time: 7.0 months; Nivolumab median follow-up time: 7.1 months

| **End point values** | Andecaliximab + Nivolumab | Nivolumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 5 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (1.807 to 99999) | 99999 (2.037 to 99999) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants who Experienced Treatment-emergent Adverse Events (TEAEs)

| End point title | Percentage of Participants who Experienced Treatment-emergent Adverse Events (TEAEs) |
|---|---|

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical study participants administered a medicinal product, which does not necessarily have a causal relationship with the treatment. TEAEs are events that are defined as AEs with onset dates on or after the first dose of andecaliximab/nivolumab and up to 30 days after permanent discontinuation of andecaliximab or 5 months after permanent discontinuation of nivolumab, or led to premature discontinuation of andecaliximab or nivolumab. The Safety Analysis Set included all participants who received at least 1 dose of study drug.

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

End point timeframe:

Andecaliximab: First dose date up to last dose (maximum: 101 weeks) + 30 days; Nivolumab: First dose date up to last dose (maximum: 101 weeks) + 5 months

| End point values | Andecaliximab + Nivolumab | Nivolumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 | 70 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 98.6 | 97.1 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants who Experienced Treatment-emergent Laboratory Abnormalities

| End point title | Percentage of Participants who Experienced Treatment-emergent Laboratory Abnormalities |
|---|---|

End point description:

Treatment-emergent (Chemistry, Hematology, Coagulation, and Urinalysis) laboratory abnormalities were graded per Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 where: 0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Potentially Life Threatening. Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of the last dose of andecaliximab plus 30 days or nivolumab plus 5 months. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent. Percentage of participants with any postbaseline Grade 1 or higher laboratory abnormality is reported. Participants in the Safety Analysis Set with available data were analyzed. aPTT = activated partial thromboplastin time, INR = international normalized ratio.

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

End point timeframe:

Andecaliximab: First dose date up to last dose (maximum: 101 weeks) + 30 days; Nivolumab: First dose date up to last dose (maximum: 101 weeks) + 5 months

| End point values | Andecaliximab + Nivolumab | Nivolumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 | 70 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Alanine Aminotransferase Increased (n=70, 70) | 20.0 | 27.1 | | |
| Alkaline Phosphatase Increased | 45.1 | 40.0 | | |
| Aspartate Aminotransferase Increased (n=70, 70) | 30.0 | 28.6 | | |
| Blood Bilirubin Increased | 8.5 | 11.4 | | |
| Chronic Kidney Disease | 16.9 | 25.7 | | |
| Creatinine Increased | 1.4 | 7.1 | | |
| Hyperglycemia | 22.5 | 18.6 | | |
| Hyperkalemia (n=70, 70) | 7.1 | 5.7 | | |
| Hypermagnesemia | 2.8 | 1.4 | | |
| Hypoalbuminemia | 35.2 | 38.6 | | |
| Hypoglycemia | 11.3 | 4.3 | | |
| Hypokalemia (n=70, 70) | 10.0 | 11.4 | | |

| | | | | |
|---|---|---|---|---|
| Hypomagnesemia | 5.6 | 4.3 | | |
| Hyponatremia | 28.2 | 40.0 | | |
| Hypophosphatemia | 11.3 | 8.6 | | |
| Lipase Increased | 11.3 | 8.6 | | |
| Serum Amylase Increased | 9.9 | 7.1 | | |
| aPTT Prolonged (n=39, 31) | 2.6 | 19.4 | | |
| INR Increased (n=39, 32) | 2.6 | 12.5 | | |
| Anemia (n=71, 69) | 53.5 | 56.5 | | |
| Lymphocytes, Typical Count Decreased (n=71, 69) | 35.2 | 27.5 | | |
| Lymphocytes, Typical Count Increased (n=71, 69) | 4.2 | 0 | | |
| Neutrophil Count Decreased (n=71, 69) | 5.6 | 5.8 | | |
| Platelet Count Decreased (n=71, 69) | 8.5 | 5.8 | | |
| White Blood Cell Decreased (n=71, 69) | 9.9 | 7.2 | | |
| Proteinuria (Dipstick) (n=68, 67) | 29.4 | 31.3 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Deaths:Andecaliximab + Nivolumab median follow-up time 28.2 months; Nivolumab median follow-up time 28.4 months; AEs: Andecaliximab: First dose to last dose (maximum: 101 weeks) + 30 days; Nivolumab: First dose to last dose (maximum: 101 weeks) + 5 months

Adverse event reporting additional description:

Deaths: The Intent-to Treat Analysis Set included all participants who were randomized in the study. Adverse Events: The Safety Analysis Set included all participants who received at least 1 dose of study drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Andecaliximab + Nivolumab |

Reporting group description:

Andecaliximab 800 mg administered via intravenous (IV) infusion plus nivolumab 3 mg/kg administered via IV infusion every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent (up to 34 weeks at the time of the primary efficacy analysis; up to 101 weeks at the time of the safety follow-up analysis).

| | |
|---|---|
| Reporting group title | Nivolumab |

Reporting group description:

Nivolumab 3 mg/kg administered via IV infsion every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent (up to 41 weeks at the time of the primary efficacy analysis; up to 97 weeks at the time of the safety follow-up analysis).

| Serious adverse events | Andecaliximab + Nivolumab | Nivolumab | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 42 / 71 (59.15%) | 38 / 70 (54.29%) | |
| number of deaths (all causes) | 61 | 62 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Euthanasia | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Complication associated with device | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenia gravis | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 4 / 70 (5.71%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal disorder | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 6 / 70 (8.57%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 4 / 70 (5.71%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 3 / 70 (4.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastric perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastric stenosis | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneal haemorrhage | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hypophysitis | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polymyalgia rheumatica | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 3 / 70 (4.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |

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|---|---|---|---|
| Sepsis | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdiaphragmatic abscess | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Andecaliximab + Nivolumab | Nivolumab | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 66 / 71 (92.96%) | 62 / 70 (88.57%) | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 7 / 70 (10.00%) | |
| occurrences (all) | 5 | 8 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 4 / 70 (5.71%) | |
| occurrences (all) | 4 | 4 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 4 / 70 (5.71%) | |
| occurrences (all) | 4 | 4 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 2 / 70 (2.86%) | |
| occurrences (all) | 5 | 2 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 71 (8.45%) | 8 / 70 (11.43%) | |
| occurrences (all) | 6 | 9 | |
| Headache | | | |
| subjects affected / exposed | 6 / 71 (8.45%) | 6 / 70 (8.57%) | |
| occurrences (all) | 6 | 7 | |
| Paraesthesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 71 (1.41%) | 4 / 70 (5.71%) | |
| occurrences (all) | 1 | 4 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 14 / 71 (19.72%) | 14 / 70 (20.00%) | |
| occurrences (all) | 16 | 18 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 22 / 71 (30.99%) | 25 / 70 (35.71%) | |
| occurrences (all) | 27 | 29 | |
| Asthenia | | | |
| subjects affected / exposed | 21 / 71 (29.58%) | 12 / 70 (17.14%) | |
| occurrences (all) | 29 | 12 | |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 71 (14.08%) | 4 / 70 (5.71%) | |
| occurrences (all) | 11 | 5 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 6 / 71 (8.45%) | 6 / 70 (8.57%) | |
| occurrences (all) | 6 | 6 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 4 / 70 (5.71%) | |
| occurrences (all) | 1 | 4 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 27 / 71 (38.03%) | 17 / 70 (24.29%) | |
| occurrences (all) | 34 | 20 | |
| Vomiting | | | |
| subjects affected / exposed | 22 / 71 (30.99%) | 18 / 70 (25.71%) | |
| occurrences (all) | 30 | 21 | |
| Constipation | | | |
| subjects affected / exposed | 18 / 71 (25.35%) | 18 / 70 (25.71%) | |
| occurrences (all) | 20 | 21 | |
| Abdominal pain | | | |
| subjects affected / exposed | 11 / 71 (15.49%) | 16 / 70 (22.86%) | |
| occurrences (all) | 11 | 21 | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 71 (19.72%) | 9 / 70 (12.86%) | |
| occurrences (all) | 18 | 23 | |
| Dysphagia | | | |
| subjects affected / exposed | 12 / 71 (16.90%) | 8 / 70 (11.43%) | |
| occurrences (all) | 13 | 9 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 11 / 71 (15.49%) | 2 / 70 (2.86%) | |
| occurrences (all) | 13 | 2 | |
| Ascites | | | |
| subjects affected / exposed | 7 / 71 (9.86%) | 4 / 70 (5.71%) | |
| occurrences (all) | 8 | 4 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 6 / 71 (8.45%) | 2 / 70 (2.86%) | |
| occurrences (all) | 7 | 2 | |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 5 / 70 (7.14%) | |
| occurrences (all) | 2 | 5 | |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 2 / 70 (2.86%) | |
| occurrences (all) | 5 | 2 | |
| Abdominal distension | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 2 / 70 (2.86%) | |
| occurrences (all) | 4 | 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 10 / 71 (14.08%) | 9 / 70 (12.86%) | |
| occurrences (all) | 10 | 10 | |
| Cough | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 8 / 70 (11.43%) | |
| occurrences (all) | 5 | 8 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 6 / 70 (8.57%) | |
| occurrences (all) | 4 | 6 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Insomnia | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 9 / 70 (12.86%) | |
| occurrences (all) | 3 | 9 | |
| Anxiety | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 2 / 70 (2.86%) | |
| occurrences (all) | 5 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 11 / 71 (15.49%) | 5 / 70 (7.14%) | |
| occurrences (all) | 11 | 6 | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 6 / 70 (8.57%) | |
| occurrences (all) | 5 | 6 | |
| Myalgia | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 4 / 70 (5.71%) | |
| occurrences (all) | 3 | 4 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 4 / 70 (5.71%) | |
| occurrences (all) | 0 | 4 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 71 (9.86%) | 1 / 70 (1.43%) | |
| occurrences (all) | 7 | 1 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 4 / 70 (5.71%) | |
| occurrences (all) | 4 | 4 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 0 / 70 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 24 / 71 (33.80%) | 20 / 70 (28.57%) | |
| occurrences (all) | 29 | 26 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 7 / 70 (10.00%) | |
| occurrences (all) | 6 | 8 | |

| | | | |
|---|---|---|---|
| Dehydration | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 5 / 70 (7.14%) | |
| occurrences (all) | 2 | 5 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 5 / 70 (7.14%) | |
| occurrences (all) | 2 | 5 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 4 / 70 (5.71%) | |
| occurrences (all) | 2 | 4 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 4 / 70 (5.71%) | |
| occurrences (all) | 1 | 4 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 1 / 70 (1.43%) | |
| occurrences (all) | 5 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 13 June 2016 | • Modified eligibility tissue requirements for PD-L1 stratification and made a new pretreatment biopsy optional.<br>• Updated chemistry analytes that were tested by the central laboratory.<br>• Clarified urine pregnancy procedures in the schedule of assessments.<br>• Modified eligibility requirements based on central labs.<br>• Clarified dosing information for nivolumab in the Dosage and Administration Section. |
| 02 August 2016 | • Added Thyroid function tests o the schedule of assessments and the body of the protocol to maintain consistency with protocol.<br>• Added an exclusion criterion to exclude participants with history of bone marrow, stem cell, or allogenic organ transplantation. |
| 16 June 2017 | Updated the section regarding Discontinuation Criteria for nivolumab to refer to the local nivolumab Summary of Product Characteristics (SmPC) for dose adjustments, AE management guidance, and discontinuation criteria. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported